A Dissertation on

A STUDY ON PREVALENCE OF HYPOTHYROIDISM (CLINICAL/SUBCLINICAL) IN DIABETES MELLITUS AND CORRELATION OF HbA1C LEVELS WITH TSH LEVELS CHENNAI – 600 001.

Submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY
CHENNAI – 600032

In partial fulfilment of the Regulations
for the Award of the Degree of

M.D. BRANCH - I

GENERAL MEDICINE

DEPARTMENT OF GENERAL MEDICINE
STANLEY MEDICAL COLLEGE
CHENNAI – 600 001

APRIL 2015

CERTIFICATE BY THE INSTITUTION

This is to certify that **Dr. DILIP HARINDRAN VALLATHOL,** Post - Graduate Student (May 2012 TO April 2015) in the Department of General Medicine STANLEY MEDICAL COLLEGE, Chennai- 600 001, has done this dissertation on "**A STUDY ON PREVALENCE OF HYPOTHYROIDISM (CLINICAL / SUBCLINICAL) IN DIABETES MELLITUS AND CORRELATION OF HbA1C LEVELS WITH TSH LEVELS, CHENNAI – 600001"** under my guidance and supervision in partial fulfillment of the regulations laid down by the Tamilnadu Dr. M. G. R. Medical University, Chennai, for M.D. (General Medicine), Degree Examination to be held in April 2015.

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CERTIFICATE BY THE GUIDE

This is to certify that **Dr. DILIP HARINDRAN VALLATHOL,** Post - Graduate Student (MAY 2012 TO APRIL 2015) in the Department of General Medicine STANLEY MEDICAL COLLEGE, Chennai- 600 001, has done this dissertation on "**A STUDY ON PREVALENCE OF HYPOTHYROIDISM (CLINICAL / SUBCLINICAL) IN DIABETES MELLITUS AND CORRELATION OF HbA1C LEVELS WITH TSH LEVELS, CHENNAI – 600001"** under my guidance and supervision in partial fulfillment of the regulations laid down by the TamilnaduDr.M.G.R. Medical University, Chennai, for M.D. (General Medicine), Degree Examination to be held in April 2015.

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DECLARATION

I, **Dr. DILIP HARINDRAN VALLATHOL,** declare that I carried out this work on "**A STUDY ON PREVALENCE OF HYPOTHYROIDISM (CLINICAL / SUBCLINICAL) IN DIABETES MELLITUS AND CORRELATION OF HbA1C LEVELS WITH TSH LEVELS, CHENNAI - 600001**" at the Toxicology unit of IMCU and Medical wards of Government Stanley Hospital during the period February 2014 to September 2014. I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, or diploma to any other university, board either in India or abroad.

This is submitted to The Tamilnadu DR. M. G. R. Medical University, Chennai in partial fulfilment of the rules and regulation for the M. D. Degree examination in General Medicine.

DR. DILIP HARINDRAN VALLATHOL

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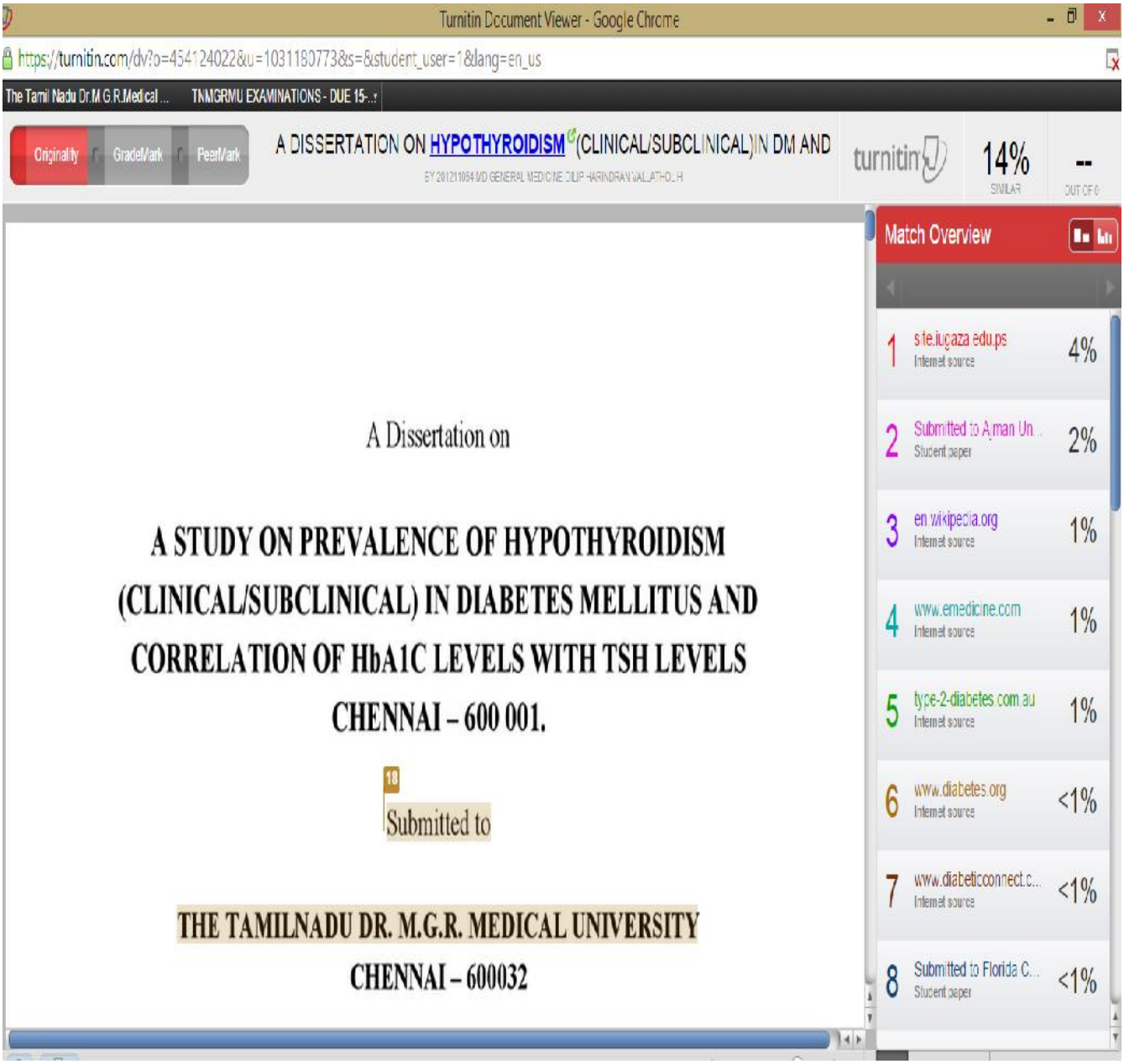
Last but not the least; I sincerely thank all those **patients** who participated in this study, for their co-operation.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CONTENTS

ABBREVIATIONS

T3	:	T3-Triiodothyronine
T4	:	T4-Thyroxine
TSH	:	Thyroid Stimulating Hormone
HbA1c	:	Glycosylated Haemoglobin
FPG	:	Fasting Plasma Glucose
PPBG	:	Post Prandial Blood Glucose
AMPK	:	Adenosine Monophosphate Kinase
LDL	:	Low Density Lipoproteins
TG	:	Triglycerides
AGE	:	Advanced Glycosylation End Products
DCCT	:	Diabetes Control and Complication Trial
HDL	:	High density lipoproteins
GLUT	:	Glucose Transporter
AgRP	:	Agouti related Peptide
POMC	:	Pro opio melanocortin
CPT-1	:	Carnitine Palmitoyl Transferase 1
ADA	:	American Diabetes Association
CHF	:	Congestive Heart Failure

I. AIMS AND OBJECTIVES

The main objectives of the study are as follows:

1. To study the prevalence of Hypothyroidism (Clinical/Subclinical) in Diabetic patients
2. To study the correlation of HbA1c levels with TSH levels

II. MATERIALS AND METHODS

PLACE OF STUDY

Stanley Medical College and Hospital, Chennai:

Department of General Medicine, Endocrinology OPD, Medical wards

SAMPLE SIZE: 50

DURATION

February 2014 - September 2014.

STUDY DESIGN

Prospective Observational Study

ETHICAL COMMITTEE APPROVAL

Ethical committee approval was obtained for the study

PATIENT SELECTION

Inclusion Criteria:

1. Any patient coming with history of type 2 Diabetes Mellitus of more than 3 years duration with or without Hypothyroidism.
2. Any patient on treatment for Hypothyroidism with history of type 2 Diabetes.

Exclusion Criteria:

1. Patients with type 2 Diabetes Mellitus for less than 3 years duration.
2. Patients in Hyperglycaemic emergencies.
3. Patients with pervious history of Thyroid surgery.

METHODOLOGY

Patients coming with history of type 2 diabetes mellitus with or without history hypothyroidism of more than 3 years duration or patients on treatment for hypothyroidism with history of diabetes mellitus presenting to OPDs or admitted in wards from February 2014 to September 2014 are included in the study. Patients are subjected to symptom analysis, clinical examination, blood investigations including HBA1C and TSH levels. The newly diagnosed patients of hypothyroidism in diabetes were treated with thyroxine for three months and followed up with TSH and HBa1c levels.

III. CONCLUSION

Diabetes Mellitus and hypothyroidism are very closely related to each other and both are associated with several metabolic abnormalities. There are many common features in both these endocrine disorders.

The normalization of TSH levels leads to a reduction in postprandial glucose levels, CRP, HbA1c and lipids. This indicates a significant effect of treatment with L-thyroxine on glycemic control in patients with subclinical hypothyroidism.

Determination of TSH is accurate, accessible, safe and inexpensive test to diagnose subclinical hypothyroidism. Determining the level of TSH can be used to define the risk of the occurrence of various complications (osteoporosis, cardiovascular disease, depression) for different intervals between TSH.

Subclinical hypothyroidism is quite hard to diagnose. In practice this is often overlooked. Adequate diagnosis requires conducting extensive laboratory tests other than routine as the TSH test. Monitoring of body temperature and careful monitoring of clinical signs, then well taken case history helps to faster and easier detection of this disease in medical practice.

My study revealed a strong correlation between duration of diabetes and hypothyroidism, FBS values and hypothyroidism.Hba1c before and after thyroxine, TSH before and after thyroxine also revealed a strong

correlation($p<.05$).The main part of my study which revealed a strong correlation between Hba1c and TSH levels.

As per the previous studies (as in citations) and my study, I can conclude that there was high prevalence of hypothyroidism in diabetes mellitus and there was correlation between Hba1c and TSH levels.

More studies with similar indices have to be performed to confirm the study results. I can also conclude that doing a TSH levels in patients of diabetes mellitus is warranted.

KEY WORDS: Hypothyroidism, subclinical hypothyroidism, Diabetes mellitus,Hba1c, fasting blood sugar, TSH, thyroxine.

I. INTRODUCTION

Diabetes and hypothyroidism are common metabolic disorders. Both diabetes and hypothyroidism are interrelated.The hallmarks of hypothyroidism are decreased absorption of glucose from the intestinal tract along with increased accumulation of glucose in the periphery with decreased glucose production from the liver and decreased use of glucose. For those who have subclinical or overt hypothyroidism, insulin resistance causes glucose stimulated increase in insulin secretion. Moreover those with subclinical hypothyroidism have an independent risk for insulin resistance especially in the muscle and adipose tissue. There is a definite link between hyperinsulinemia, resistance to insulin and subclinical hypothyroidism. There are numerous mechanisms through which subclinical hypothyroidism and insulin resistance causes derangement of glycemic control. Thus the significance of treating subclinical hypothyroid patients with L thyroxin for better glycaemic control is well indicated. Some studies have also shown positive effect of metformin therapy in control of thyroid hormone levels.

II. REVIEW OF LITERATURE

HISTORICAL REVIEW

Diabetes:

The very first person to give a complete clinical description of diabetes was the Greek physician Aretaeus of Cappadocia, who found out that patients suffering from this disease passed increased amount of urine.

Avicenna (930 – 1037) gave a full description about diabetes mellitus in the book "THE CANON OF MEDICINE" detailing about the increased appetite and the diminished sexual functions in the patients, and urine of those people tasting sweet. He recognised primary as well as secondary diabetes just like Aretaeus before him.

Joseph von Mering and Oskar Minkowski, in 1889, found that when the pancreas in the dogs was removed, they developed signs and symptoms of diabetes mellitus and they died soon afterwards. This clearly pointed out the involvement of pancreas in diabetes mellitus. Sir Edward Albert Sharpey-Schafer in 1910 postulated that a deficiency of a single chemical which the pancreas produces is responsible for diabetes—he proposed naming this chemical *insulin,* from the Latin *insula,* which meant island, in reference to insulin secreting islets of Langerhans in pancreas.[3]

Thyroid:

The Chinese people in 1600 BC used seaweed and sponge which was burnt for the treatment of goitre. Pliny has given an account about the prevalence of an epidemic of goitre in Alps and mentions the use of burnt seaweed as treatment for it.

Galen in 150 AD also talks about the use of burnt sponge, spongia-usta, for the treatment of goitre. He suggested that lubricating the larynx was the major function of thyroid.

Wang Hei in 1475 described the anatomy of the thyroid gland and said that the remedy for goitre must be dried goitre. About fifty years later, Paracelsus said that goitre was due to the mineral impurities present in water. Thomas Wharton in1656 coined the name of the gland as THYROID meaning SHIELD.

Robert James Graves, doctor of Irish origin published a paper on exophthalmic goitre. Exophthalmic goitre is known as Basedow's disease in the European continent. Karl Adolph Basedow in 1840 had independently described this entity.

Only in the last century, the idea that thyroid produced an iodine containing substance was investigated, and Edward Calvin Kendall isolated thyroxine in 1914 as the active principle of thyroid gland.

THYROID GLAND

Embryology:

The morphogenesis of the thyroid gland, anterior-most organ which buds from gut tube, begins with thickening of endodermal epithelium in the foregut, referred to as thyroid anlage. The human thyroid anlage is first recognizable at embryonic day 16 or 17. This median thickening deepens and forms a small pit first and then an outpouching of the endoderm adjacent to the developing myocardial cells.[6]

The primitive stalk connecting the primordium with the pharyngeal floor elongates into the thyroglossal duct. During its caudal displacement, the primordium assumes a bilobate shape, coming into contact and fusing with the ventral aspect of the fourth pharyngeal pouch when it reaches its final position at about embryonic day 50.6.[6, 7]

The thyroglossal duct undergoes dissolution and fragmentation at the second month after conception, which leaves at the origin a small dimple at the junction of middle one-third and posterior one-thirds of the tongue called the *foramen caecum.* Cells of the lower portion of duct differentiate into thyroid, forming the pyramidal lobe of the gland. At the same time, the lobes contact the ultimobranchial glands, leading to conversion of C cells into the thyroid.[7, 8]

The histologic alterations occur in the entire gland. Complex, interconnecting, cord-like arrangements of cells mixed with vascular connective tissue replaces solid epithelial mass and become tubule-like structures at third month of fetal life; shortly after that, follicular arrangements devoid of colloid appear, following which, at 13 to 14 weeks, the follicles starts to get filled with colloid.[4]

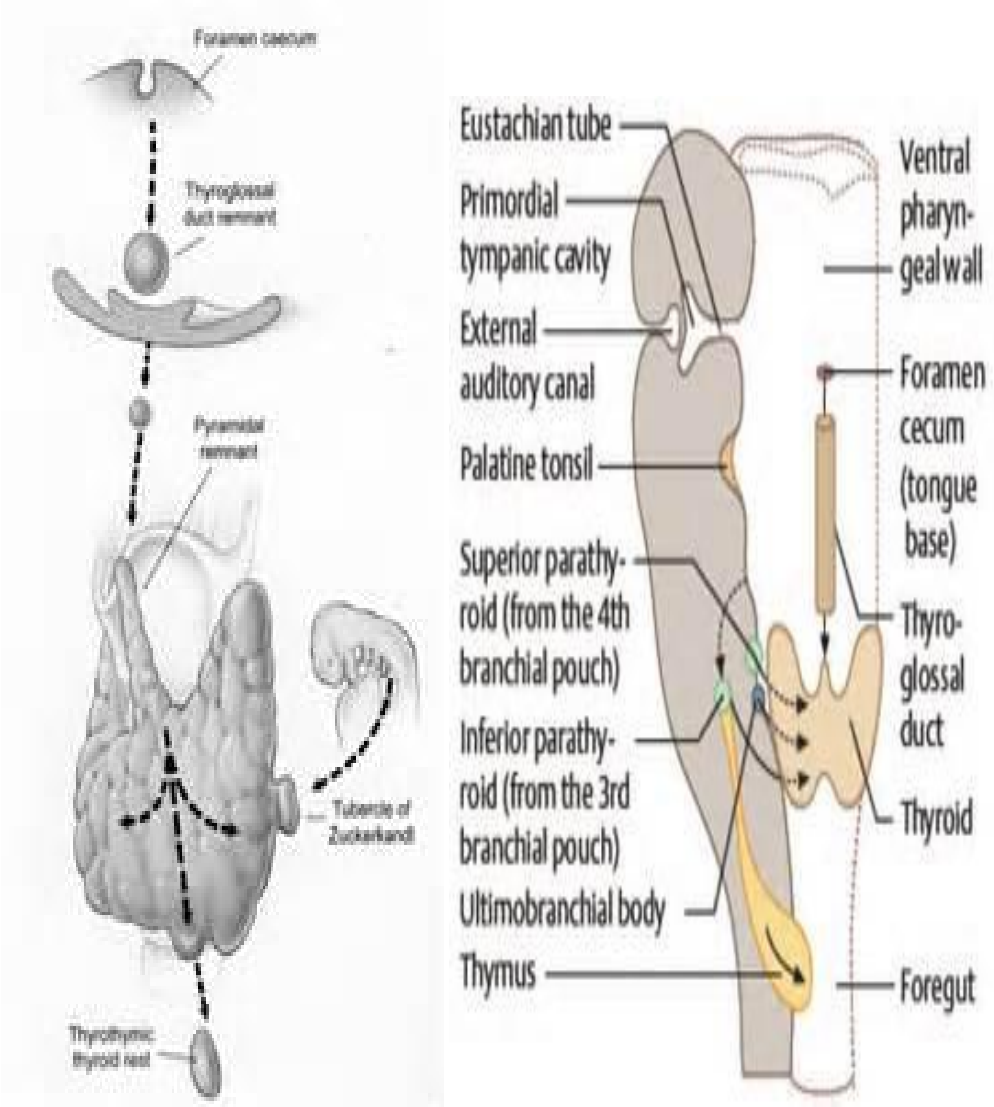


Fig: Evolution of Thyroid gland and its relation to the Branchial Arches

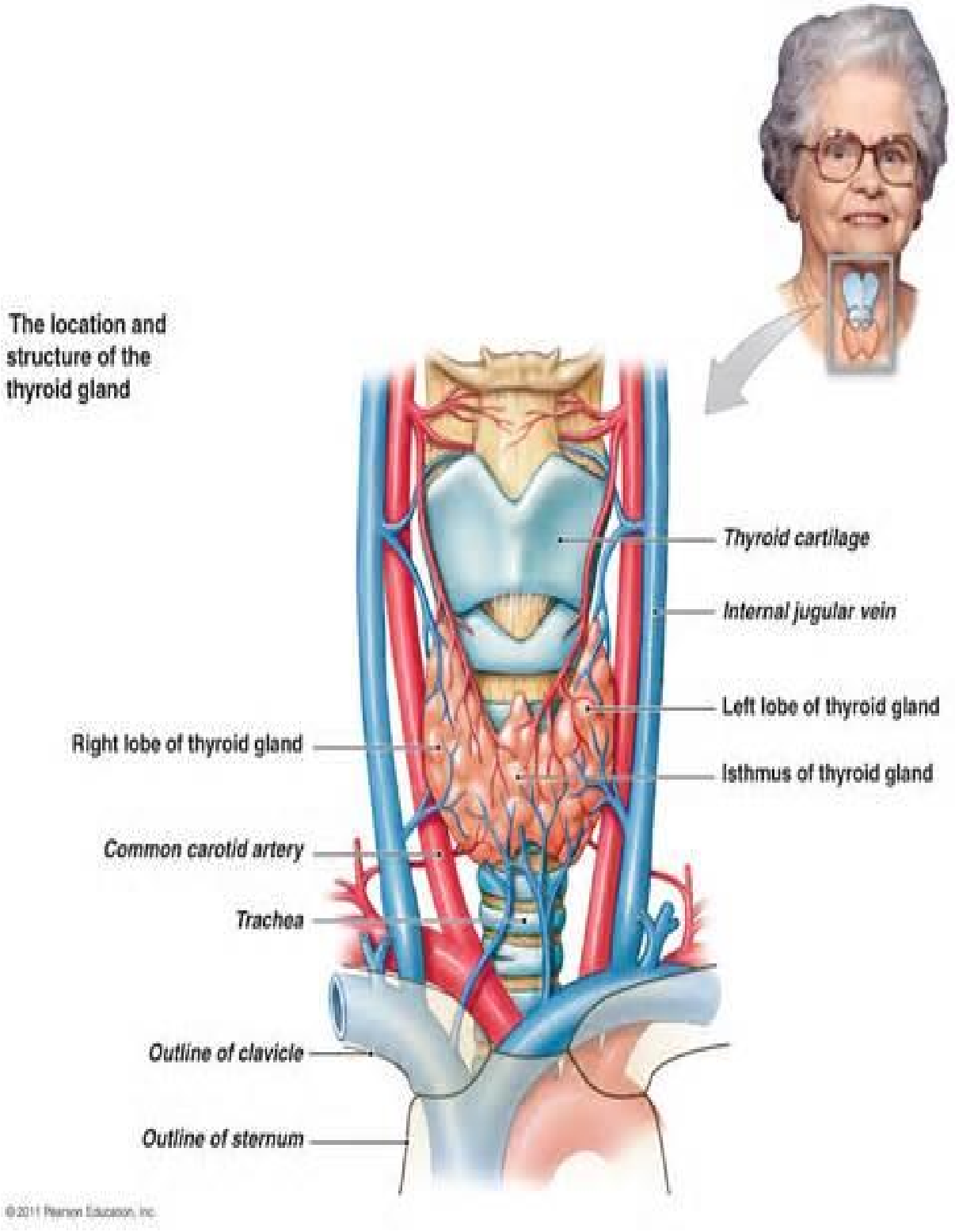


Fig: Anatomy of the Thyroid gland

Anatomy:

The thyroid (Greek *thyreos*, meaning shield, plus *eidos*, meaning form) is a red-brown, highly vascular organ located anteriorly at the lower part of the neck, which extends from the level of 5th cervical vertebra to the 1st thoracic vertebra.

The gland shape varies from H to U and it overlies the 2nd to 4th tracheal rings.[1, 6] The thyroid is one of the biggest of the endocrine organs, weighing about 15 to 20 g.

Moreover, the potential of thyroid for growing is tremendous. The enlarged thyroid, commonly termed a *goiter*, weighs hundreds of grams. The normal thyroid is made of two lobes which is joined by a thin band of tissue, the isthmus, that is approximately 0.5 cm thick, 2 cm wide, and 2 cm high.

The individual lobe normally has pointed superior pole and a poorly defined, blunt inferior pole that merges medially with the isthmus. Each lobe is about 2.0 to 2.5 cm thick and breadth at its largest diameter is approximately 4.0 cm in length.

Occasionally, if the remaining part of the gland is enlarged, a pyramidal lobe is discernible as a finger-like projection directed from the isthmus, usually on the left, just lateral to the midline. The right lobe is more vascular than the left; it is

often the bigger of the two and enlarges more in disorders associated with a diffuse increase in gland size.[6, 7]

Vascular anatomy:

The thyroid gland is supplied by the superior thyroid and inferior thyroid arteries and at sometimes by the thyroidea ima artery.[7, 8]

Estimates of thyroid blood flow range from 4 to 6 mL/minute per gram; well in excess of the blood flow to the kidney (3 mL/minute per gram).

In diffuse toxic goiter resulting from Graves' disease, blood flow may exceed 1 L/minute and may be associated with an audible bruit or even a palpable thrill.[8]

Venous drainage:

The thyroid is drained by three pairs of veins.

- The superior thyroid vein - ascends up with superior thyroid artery and it becomes a tributary to internal jugular vein.
- The middle thyroid vein - courses lateral to internal jugular vein.
- The inferior thyroid vein - The right passes anterior to innominate artery to right of brachiocephalic vein. The left drains into the left brachiocephalic vein.

At times, both inferior veins join to form a common trunk which is called as the thyroid ima vein, which drains into left brachiocephalic vein.[7, 8]

Lymphatic drainage:

The lymph from the thyroid gland flows to periglandular nodes, prelaryngeal nodes, pretracheal nodes and paratracheal nodes along with the recurrent laryngeal nerve and finally into the mediastinal nodes.[7, 8]

The major hormones secreted by thyroid gland are thyroxine (T4), triiodothyronine (T3), and calcitonin. T3 is also formed by de-iodination of T4 in the peripheral tissues. Both T3 and T4 are formed from the same iodine containing amino acids. Small amounts of reverse triiodothyronine (RT3) are also formed, which is inactive. T3 is more active than T4.

Naturally occurring forms of T4 are L isomers.[1, 6] Of the total metabolically active hormones produced by the thyroid gland around 93% is T4 and around 7 % is T3. Eventually all the T4 is converted to T3 in the tissues. Even though the functions of T3 and T4 are qualitatively the same they differ in onset and intensity of action. T3 is 4 times more potent than T4, but it is present in blood in much lesser amounts and lasts for shorter duration of time than T4.[9]

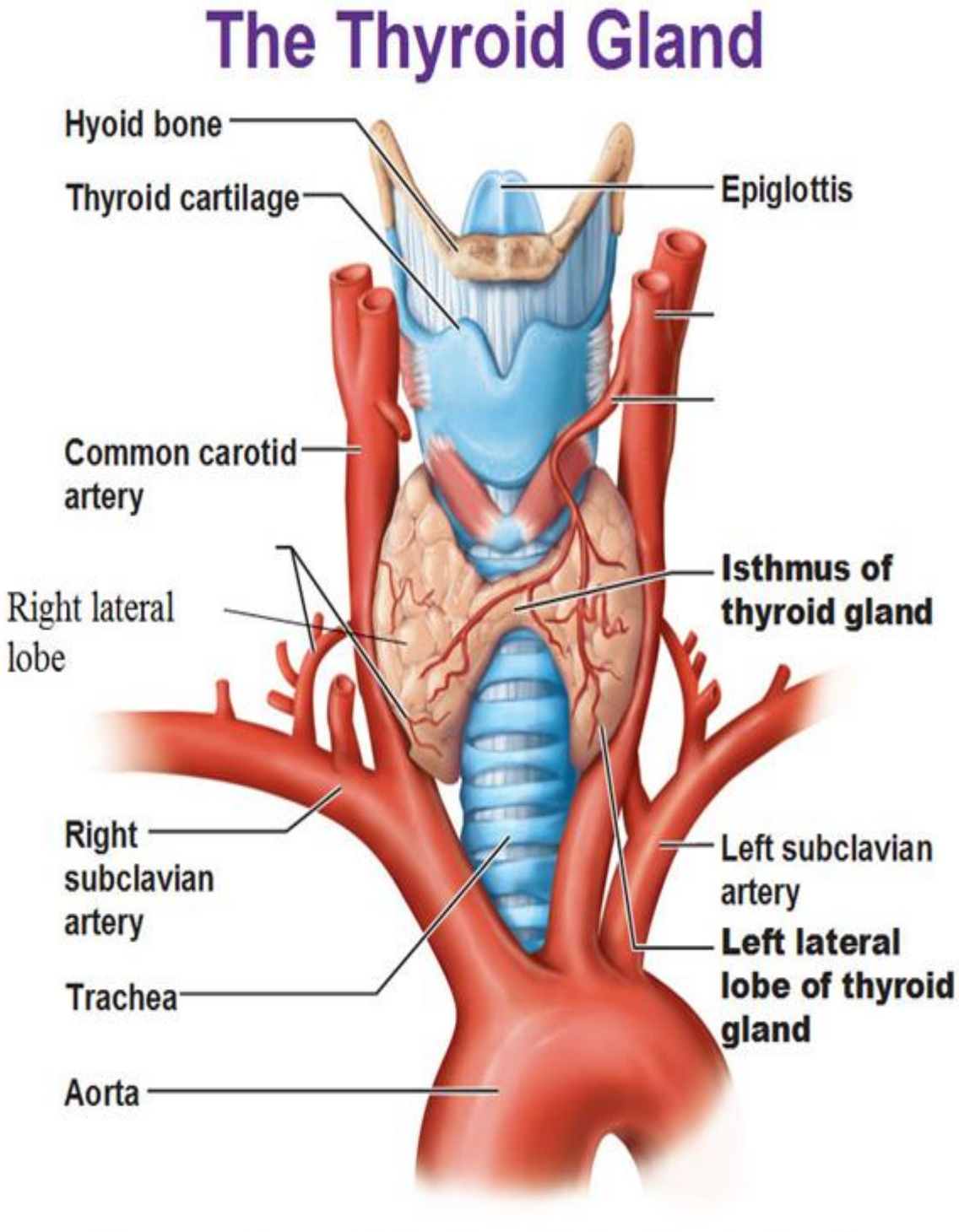


Fig: Vascular Anatomy of the Thyroid Gland

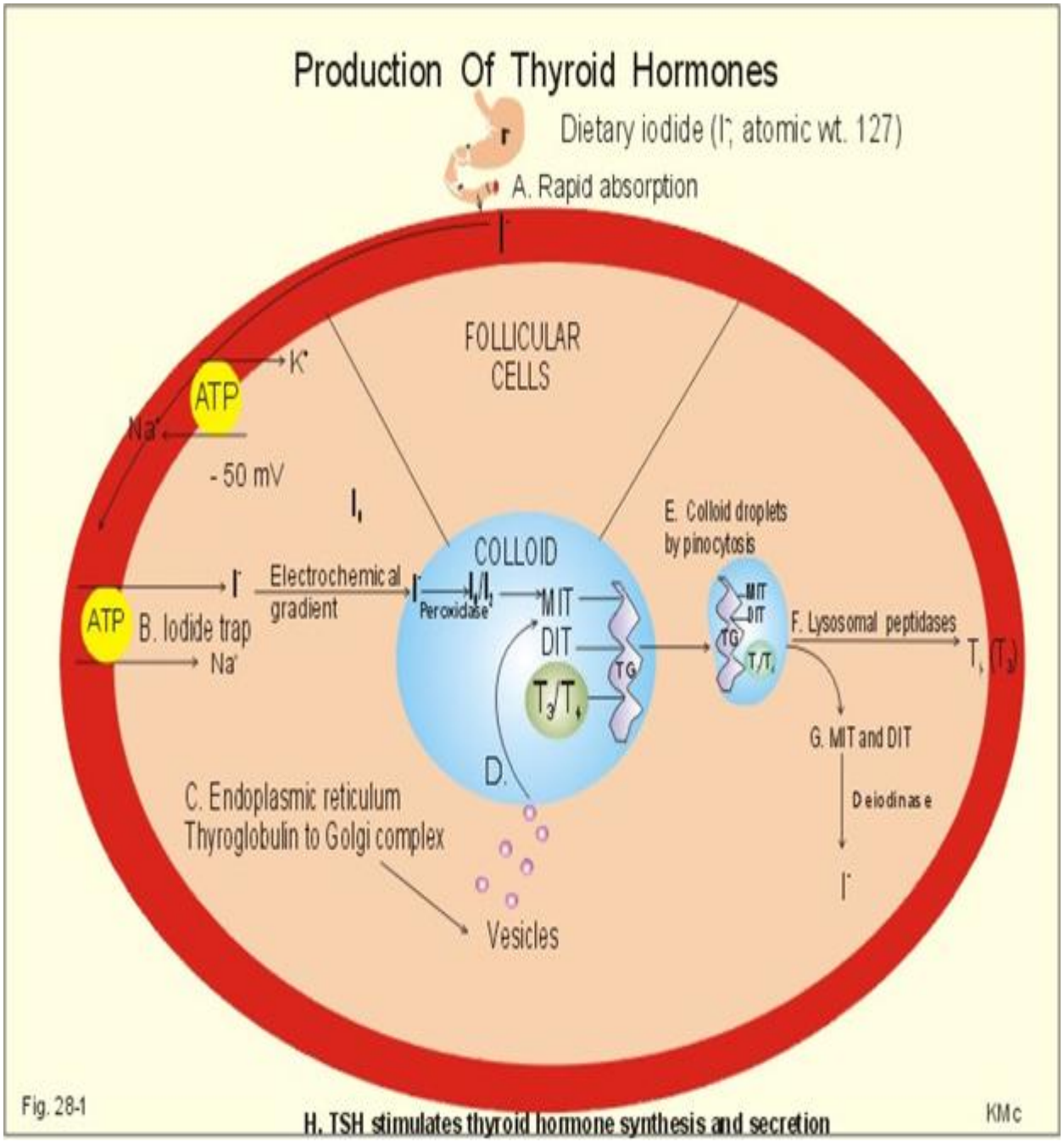


Fig: Physiology of the Thyroid gland

Iodide Pump (Iodide Trapping):

Transport of I^- ions from the blood into the thyroid gland follicles is the first step in the formation of thyroid hormones. The basal membrane of the thyroid cell has unique ability to actively pump the iodide into the interior of the thyroid cell. This is known as *iodide trapping*.[1, 9]

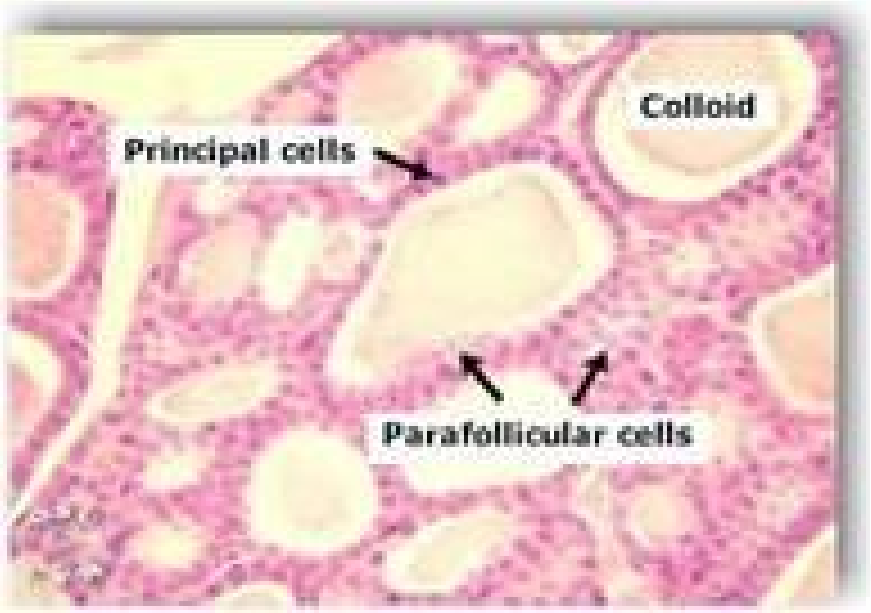


Fig: Thyroid gland Histology

Thyroglobulin and Chemistry of Thyroxine and Triiodothyronine Formation:

Formation and Secretion of Thyroglobulin by the Thyroid Cells

The cells of the thyroid gland are protein producing glandular cells. The endoplasmic reticulum and Golgi apparatus synthesize and secrete *thyroglobulin* a large glycoprotein molecule into thyroid follicle. Thyroglobulin

has a molecular weight of 335,000. Each one of the molecule of thyroglobulin has 70 tyrosine amino acids and they combine with iodine to form the thyroid hormones. During synthesis of the thyroid hormones, the thyroxine and triiodothyronine hormones formed from the tyrosine amino acids remain part of the thyroglobulin molecule

Oxidation of the Iodide Ion

The initial step in the synthesis of the thyroid hormones is conversion of the iodide ions to the *oxidized form* which is capable of combining directly with the amino acid tyrosine. Enzyme *peroxidase* and *hydrogen peroxide* promotes the oxidation of iodide .The peroxidase is attached to the apical membrane of the cell and it provides the oxidized iodine at exactly the point in the cell where the thyroglobulin goes forth from the Golgi bodies and through the cell membrane into the stored thyroid gland colloid. Thus when the peroxidase system is blocked or if it is hereditarily absent the formation of thyroid hormones becomes nil.[9]

Iodination of Tyrosine and Formation of the Thyroid Hormones- "Organification" of Thyroglobulin

The binding of iodine with the thyroglobulin molecule is known as *organification* of the thyroglobulin. Oxidized iodine will bind directly but very slowly with the amino acid tyrosine in molecular form. Oxidized iodine within

the thyroid cell is found to be associated with an enzyme called as iodinase that causes the process to occur within seconds or minutes.

As the thyroglobulin molecule is released from the Golgi apparatus iodine attaches with around $1/6^{th}$ of the tyrosine amino acids within the thyroglobulin molecule.

Tyrosine is first iodized to *monoiodotyrosine* and then to *diiodotyrosine*. During next few minutes, hours, days, more of the iodotyrosine become *coupled* with one another. The main hormonal product of coupling reaction is molecule *thyroxine*.[8]

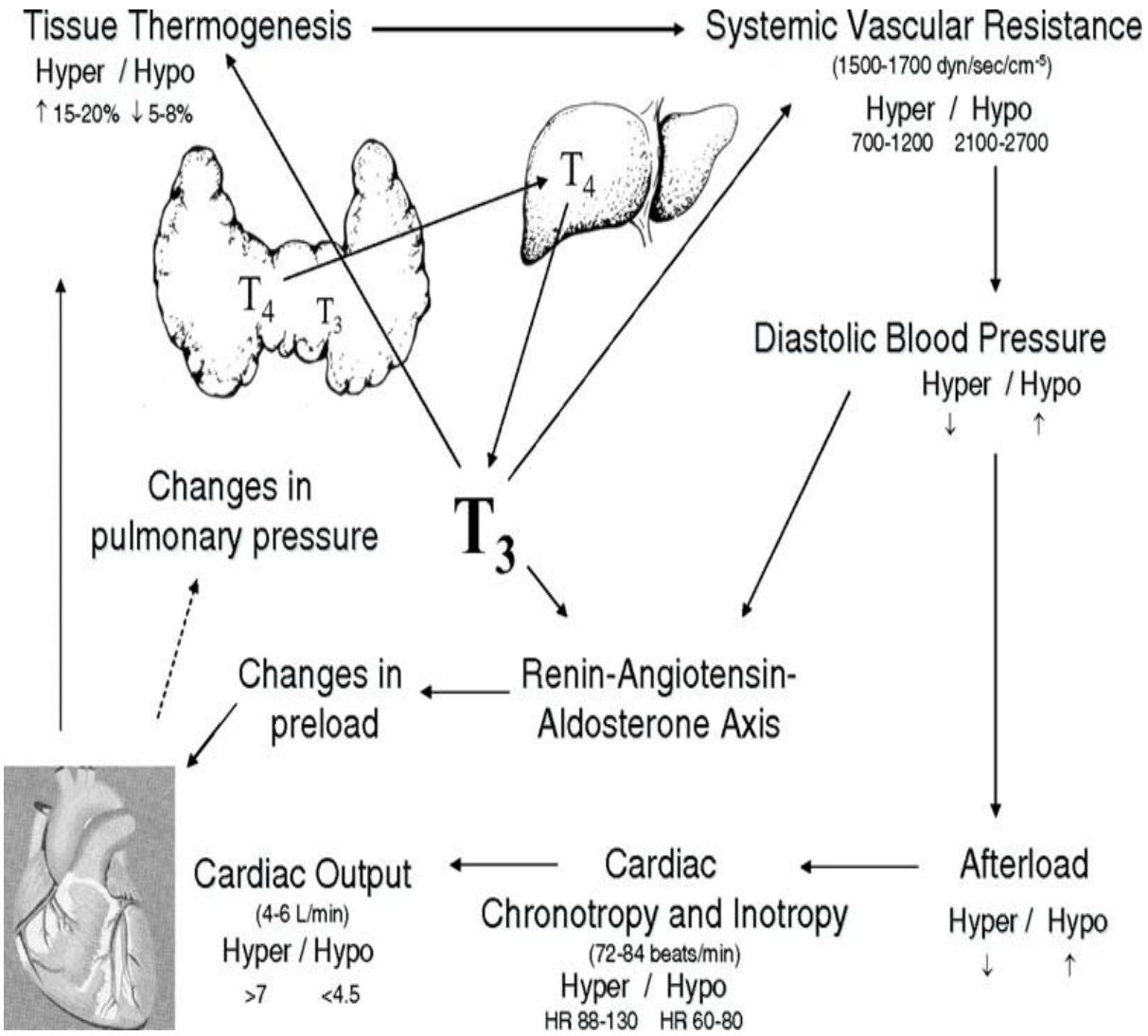


Fig: Effects of thyroid hormone on cardiovascular hemodynamics

Thyroxine remains part of thyroglobulin molecule. One molecule of monoiodotyrosine couples with another molecule of diiodotyrosine to form *triiodothyronine.*

Storage of Thyroglobulin

The thyroid gland stores large amounts of hormone. After synthesis of the thyroid hormones each thyroglobulin contains up to 30 thyroxine molecules and a few triiodothyronine molecules. The thyroid hormones are stored in the follicles in quantities which are sufficient to supply the body for two to three months.[6, 9]

Daily Rate of Secretion of Thyroxine and Triiodothyronine

Thyroxine is 93% of the thyroid hormone released from the thyroid and triiodothyronine is only 7%. In the following days after secretion half of the thyroxine is slowly de-iodinated to form more of triiodothyronine. Therefore T3 is the major hormone which is finally delivered to the tissues, about 35 micrograms of triiodothyronine per day in our body.[9, 10]

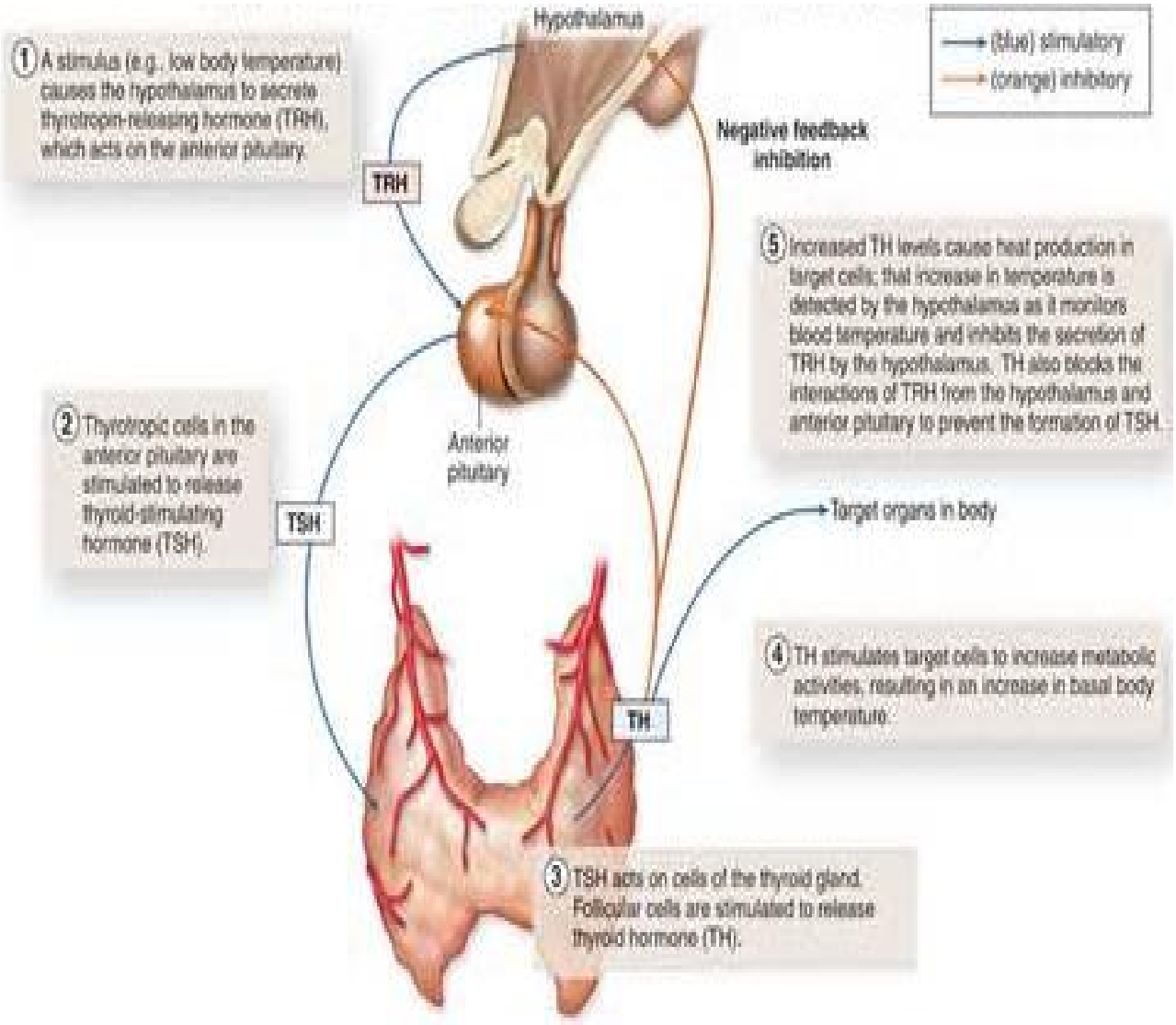


Fig: Regulation of Thyroid Hormone secretion

Thyroid Hormones Have Slow Onset and Long Duration of Action:

When thyroxine hormone is injected in large quantity it takes about 2-3 days for its action to begin and hence there is latency before thyroxine action starts.

After its action has begun it increases progressively and it takes around 10 to 12 days for it to reach its peak. After that its action decreases with a t1/2 of about 15 days and some of its activity can be detected even after 12 months. T3 acts four times faster than thyroxine with a short latent period of 6 to 12 hours and maximal cellular activity occurring within 2 to 3 days. Binding with proteins both in the plasma and in the tissue is responsible for its latency and its long duration of action.

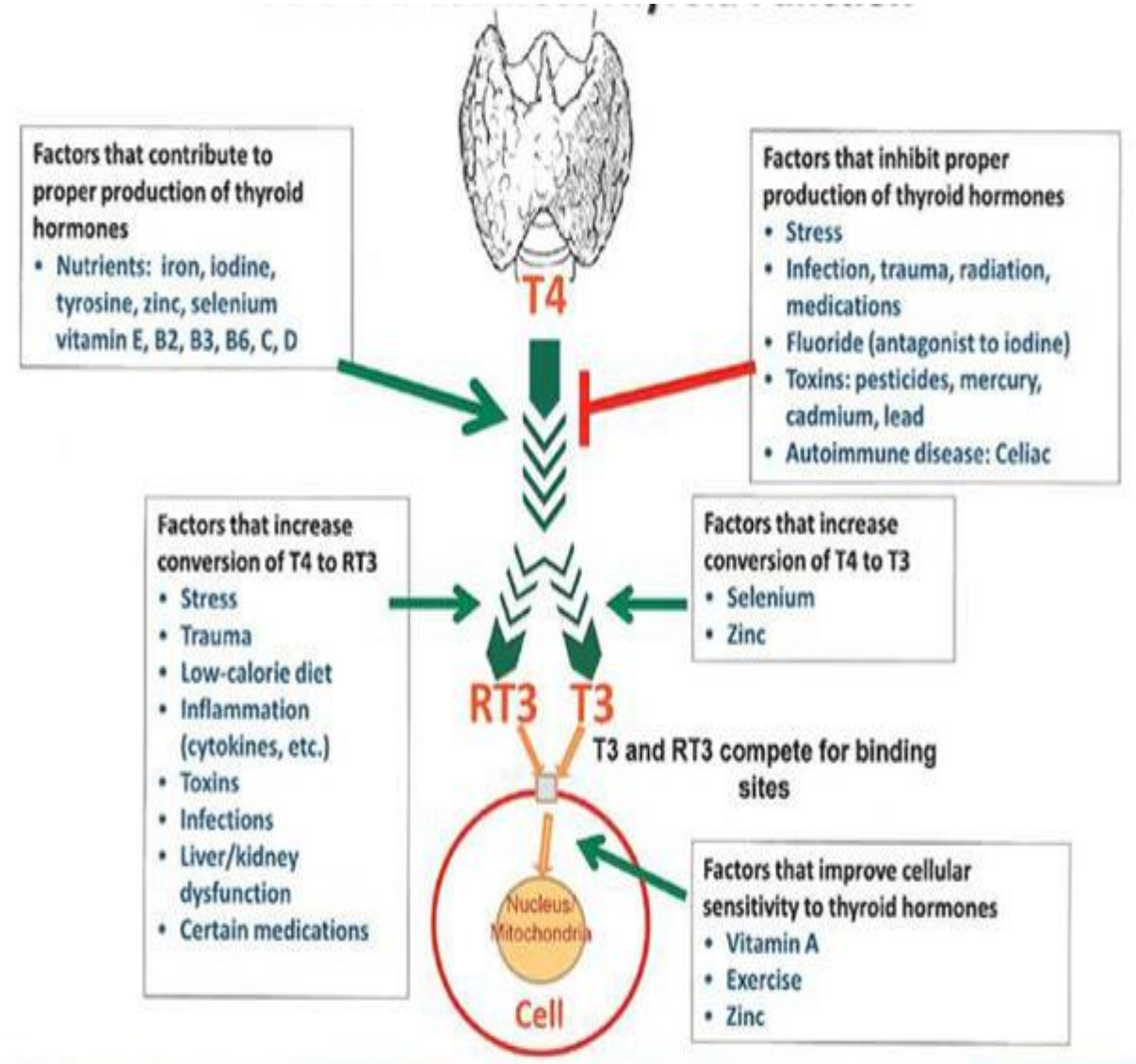


Fig: Factors that affect Thyroid function

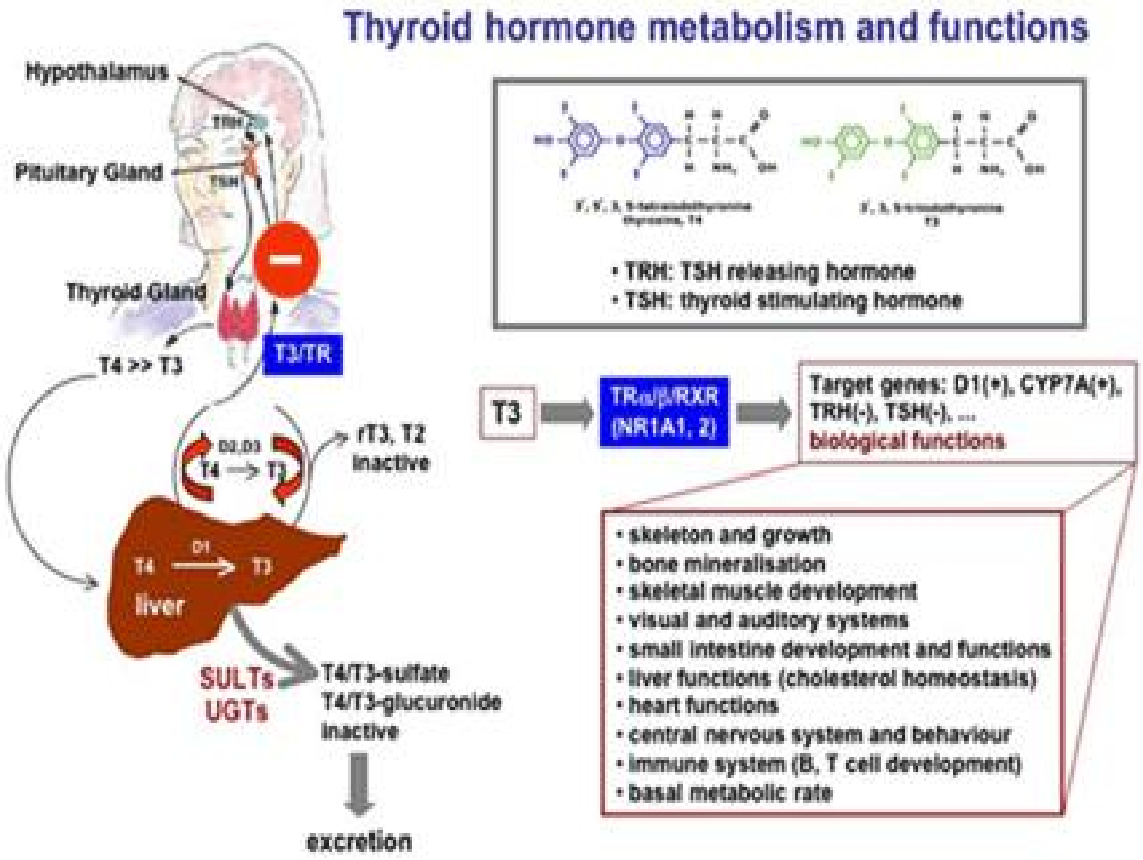


Fig: Peripheral actions of the Thyroid hormones

HYPOTHYROIDISM

Hypothyroidism (Greek, from *hypo*, under, and *thyroid*, the gland), often called underactive thyroid or low thyroid, is an endocrine abnormality which occurs commonly in which the thyroid gland is not able to produce enough thyroid hormones.

In overt primary hypothyroidism the TSH levels are high and the T_4 &T_3 levels are low.[21] It is also diagnosed in those who have a TSH value of greater than IU/L with symptoms of hypothyroid and borderline T4 values. In persons with a TSH greater than 10mIU/L it is diagnostic of hypothyroid.[21]

Subclinical hypothyroidism is a milder form characterized by an elevated serum TSH level, but a normal serum free thyroxine level.[22, 23] In adults it is diagnosed when TSH levels are greater than 5 mIU/L and less than 10mIU/L.[21]

Deficiency of iodine is the most common cause of hypothyroidism worldwide. In those areas in which iodine is sufficient, autoimmune disease (Hashimoto's thyroiditis) and other iatrogenic causes must be evaluated for.[10]

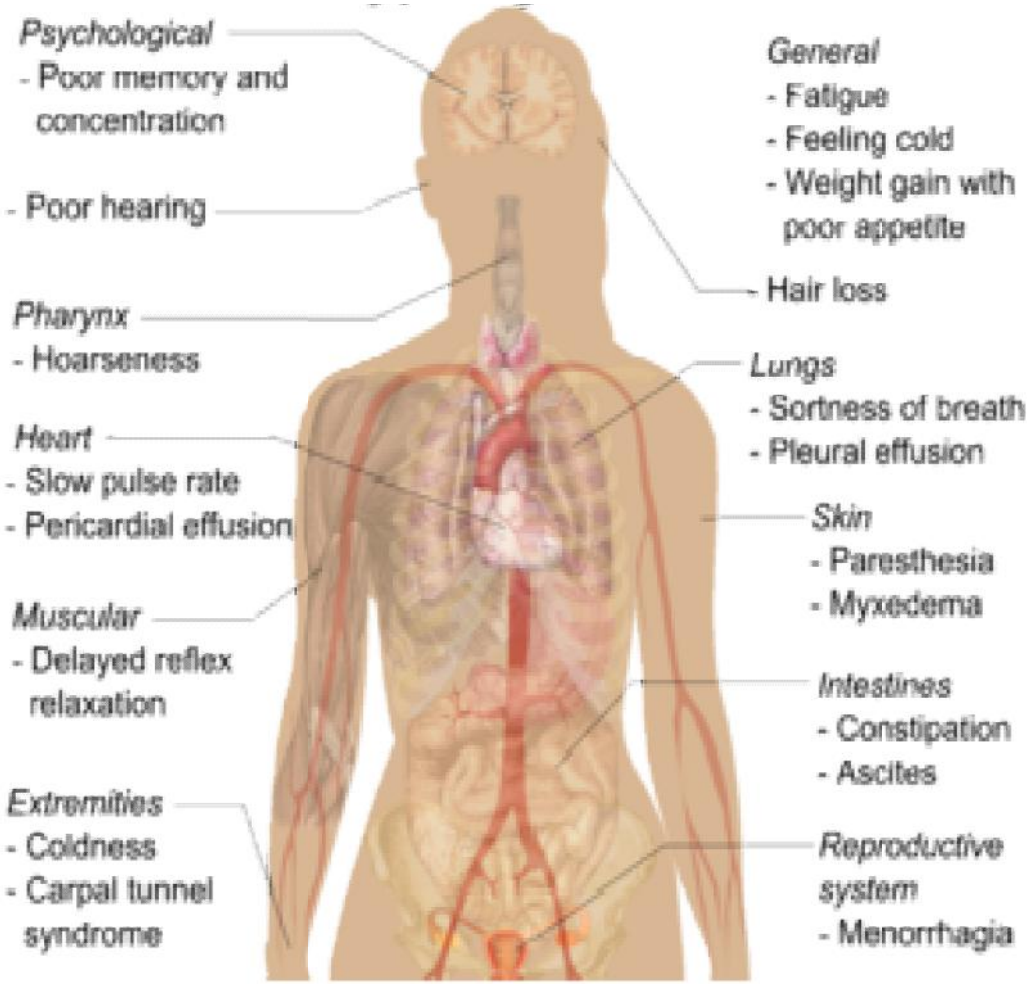


Fig: Signs and Symptoms of Hypothyroidism

Causes of Hypothyroidism	
Central (Hypothalamic/Pituitary) Hypothyroidism	
Loss of functional hypothalamic or pituitary tissue	• Tumor (pituitary adenomas, metastasis, craniopharyngioma, glioma) • Trauma (surgeries, irradiation and head injury) • Vascular (Ischemic necrosis, hemorrhage, aneurysms) • Infections (TB, abscess) • Infiltrative lesions (sarcoidosis) • Chronic lymphocytic hypophysitis • Congenital (pituitary hypoplasia, basal encephalocele)
Functional defects in TSH biosynthesis and release	• Gene mutation • Drug-induced (dopamine, glucocorticoids)
Primary Hypothyroidism	
Loss of functional thyroid tissue	• Chronic autoimmune thyroiditis (Hashimoto's thyroiditis) • Reversible autoimmune hypothyroidism (painless and postpartum thyroiditis, cytokine-induced thyroiditis). • Surgery (thyroidectomy) • Radiation (I-131 or external irradiation) • Infiltrative and infectious diseases, sub-acute thyroiditis • Congenital defects (thyroid dysgenesis)
Functional defects in thyroid hormone biosynthesis and release	• Congenital defects in thyroid hormone biosynthesis • Iodine deficiency and iodine excess • Drug-induced (antithyroid agents, lithium, amiodarone)
Peripheral (extrathyroidal) Hypothyroidism	
Resistance to thyroid hormones	• Gene mutation

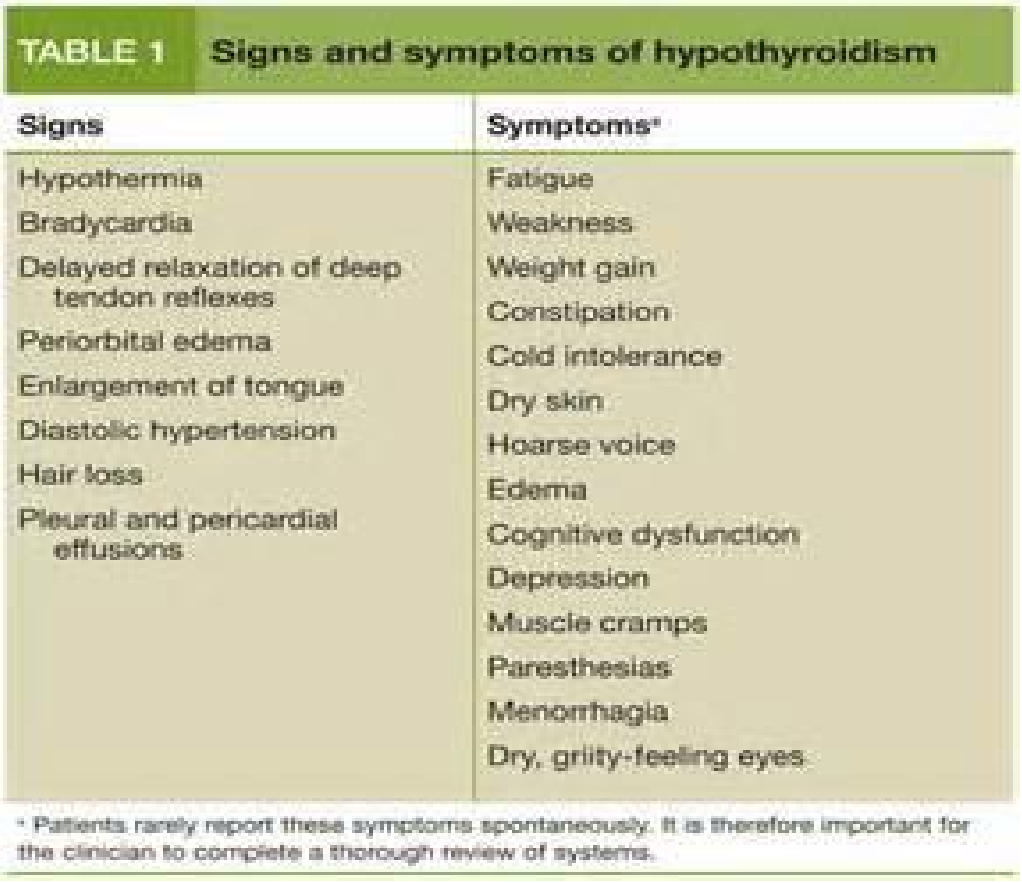


TABLE 1 Signs and symptoms of hypothyroidism

Signs	Symptoms*
Hypothermia	Fatigue
Bradycardia	Weakness
Delayed relaxation of deep tendon reflexes	Weight gain
Periorbital edema	Constipation
Enlargement of tongue	Cold intolerance
Diastolic hypertension	Dry skin
Hair loss	Hoarse voice
Pleural and pericardial effusions	Edema
	Cognitive dysfunction
	Depression
	Muscle cramps
	Paresthesias
	Menorrhagia
	Dry, gritty-feeling eyes

* Patients rarely report these symptoms spontaneously. It is therefore important for the clinician to complete a thorough review of systems.

Fig: Signs and Symptoms of hypothyroidism

Laboratory Evaluation:

If the TSH level is normal, then the diagnosis of primary hypothyroidism is ruled out. If TSH level is elevated, then the level of unbound T4 must be obtained to confirm clinical hypothyroidism. However as a screening test TSH is superior to T4 because it will detect subclinical hypothyroidism. Unbound T3 levels are normal in 25% of patients, showing adaptive de-iodinase response to hypothyroidism; hence measurement of T3 is not indicated.

Once hypothyroidism is diagnosed the presence of TPO antibodies must be searched to demonstrate the etiology. TPO antibodies are present in about 90%

of the patients who suffer from autoimmune hypothyroidism. TBII is found in 10–20% of patients however we do not perform this test routinely.[10]

Free thyroxine levels in pregnant women will be lower than expected because of decreased binding of free thyroxine to albumin and because of increased binding of free thyroxine to thyroid binding globulin. Hence total thyroxine levels must be used for diagnosis.[5] TSH values be less than the normal range in pregnancy and must be adjusted for the period of pregnancy.[5, 19]

There is a low sodium level in blood along with raised antidiuretic hormone and there is as acute worsening of kidney function due to several causes in patients suffering from very severe hypothyroidism and myxedema coma.

		Sensitive TSH		
		Normal	Low	High
T_4	Normal	Euthyroid	Subclinical/early hyperthyroidism[a] Nonthyroidal illness Drug effects L-dopa Glucocorticoids Excess T_4 therapy for hypothyroidism	Subclinical/early hypothyroidism Nonthyroidal illness Drug effects Iodine, lithium, antithyroid drugs, amiodarone Insufficient T_4 therapy for hypothyroidism
	Low	Secondary hypothyroidism[b] Nonthyroidal illness Drug effects T_3 Phenytoin Androgens Salicylates Carbamazepine Rifampin	Secondary hypothyroidism[b] Drug effects Dopamine[c] Corticosteroids[c] T_3	Primary hypothyroidism Drug effects, e.g., iodine, lithium, antithyroid drugs, amiodarone Insufficient T_4 therapy for hypothyroidism
	High	Nonthyroidal illness Acute and psychiatric illness Abnormal binding (excess TBG, familial dysalbuminemic hyperthyroxinemia, transthyretin-associated hyperthyroxinemia, some monoclonal proteins) Thyroid hormone resistance Drug effects Estrogen Iodine (drugs, contrast media) Thyroxine (factitious)	Nonthyroidal illness Acute psychiatric illness Primary hyperthyroidism[d]	TSH-secreting tumor Thyroid hormone resistance

T_3 = triiodothyronine; T_4 = thyroxine.
[a]Confirm with T_3 suppression test or lack of serum TSH response to TRH.
[b]Pituitary TSH deficiency shows deficient response to exogenous TRH. Hypothalamic TRH deficiency shows normal TSH response but may be prolonged for >30 mins.
[c]Serial monitoring or testing of serum TSH response to TRH may be needed.
[d]95% of cases; serum T_3 needed for diagnosis of T_3 thyrotoxicosis.

When thyroxine is replaced, it leads to anaemia and other derangements[1, 6]. Other laboratory findings which are abnormal in hypothyroidism are anaemia (usually normocytic or macrocytic), elevated cholesterol and triglycerides and increased creatine phosphokinase.

Entity tested	Description	Clinical utility
TSH	Thyroid-stimulating hormone or thyrotropin	• Best thyroid function screening test • Initial test for suspected thyroid disease • Used to follow patients on thyroid hormone therapy • Used in conjunction with T_4 to manage patients with Graves' disease
T_4	Serum total thyroxine	• Used to make diagnosis of underactive or overactive thyroid when TSH is abnormal • Used with TSH for monitoring patients with Graves' disease • Newborn screening test for hypothyroidism • Fairly accurate in patients with no protein abnormalities and not pregnant
FT_4	Free thyroxine is the metabolically active thyroid hormone – not bound to protein	• Should be ordered when TSH is abnormal to determine thyroid hyperfunction or hypofunction.
FTI	Free thyroxine index – measure of free T_4 determined by measuring thyroxine level and either thyroid-binding globulin or hormone-binding ratio	• Used for making the diagnosis of thyroid disease in patients with protein abnormalities and in pregnant patients • Used for monitoring therapy in above patient groups with hyperthyroidism
T_3	Serum total triiodothyronine	• Used to diagnose hyperthyroidism when TSH is low and T_4 is still normal
Thyroid antibodies	• Antithyroid peroxidase (antimicrosomal) antibodies • Antithyroglobulin antibodies	• Used to diagnose suspected Hashimoto's thyroiditis in hypothyroidism • Used to diagnose autoimmune thyroiditis or Graves' disease in hyperthyroidism

Sources: Baskin HJ et al[5]; Wilson GR and Curry RW[6]; Demers LM, Spencer CA. *Laboratory Support for the Diagnosis and Monitoring of Thyroid Disease*. American Association for Clinical Chemistry; 2002. Available at www.aacc.org/members/nacb/Archive/LMPG/ThyroidDisease/Pages/ThyroidDiseasePDF.aspx. Accessed November 19, 2009; Supit EJ, Peiris AN. Interpretation of laboratory thyroid function tests for the primary care physician. *South Med J*. 2002;95:481-485.

Treatment:

The decision for treatment with levothyroxine should take into account the expense and inconvenience of daily medication, which is not acceptable to some patients, and the possibility of overdose with levothyroxine which can exacerbate osteoporosis or cause cardiac arrhythmias. Finally, the decision to treat depends on the careful consideration of the patient's clinical situation and preference.[18]

There are no universally accepted recommendations for the treatment of subclinical hypothyroidism. Recently published guidelines do not recommend routine treatment when TSH levels are below 10 mU/L. It is vital to confirm any elevation of TSH sustained over a three month period and then only treatment is given.[17]

Prevention:

By addition of iodine to the food hypothyroidism can be prevented in the large population. Endemic childhood hypothyroidism has become extinct due to the addition of iodine to the food. Not only by promoting eating of iodine rich food like dairy and fish the iodinisation of salt which is done is several countries has played a huge role in preventing hypothyroidism.

DIABETES MELLITUS

There are two types of diabetes. The causes and risk factors for each type are as follows:

- Type 1 diabetes - in this condition the body produces very little or no insulin. The patients have to be treated with daily insulin injection. It occurs mainly in children and young people.
- Type 2 diabetes – it mostly occurs in older people. But now because of change in lifestyle modifications with more young people being obese the recent trend is occurrence of type to diabetes in younger age.

Some patients cannot be classified as type 1 or type 2.

Type 2 Diabetes:

It is the most common type of diabetes. It is also called as non insulin dependent diabetes mellitus.

People who suffer from type to diabetes mellitus make insulin the body. But the amount of insulin made in the body is insufficient to the demands. This is called as insulin resistance. Hence the transport of glucose inside the cells is impaired. So there is increase amount of glucose in the blood and the cells are exposed to high glucose which is detrimental to the cells in the following ways:

Damage to the body:

The constantly very high blood glucose levels may cause damage to the blood vessels and nerves in the eyes, heart, kidney and brain. The blood vessels may become hardened and atherosclerosis might develop in them eventually predisposing to myocardial infarction and cerebrovascular accidents.

Dehydration:

The increases blood glucose levels increases the osmolality resulting in increased urine production causing severe dehydration.

Diabetic coma (hyperosmolar nonketotic diabetic coma):

This is a life threatening complication due to increased blood glucose resulting in severe dehydration and electrolyte derangements. The patient goes into coma with negative ketones.

Common symptoms of diabetes:

- Polyuria - increased frequency of micturition
- Polydipsia - increased feeling of thirst
- Polyphagia - increased hunger
- Easy fatigability
- Vision getting blurred
- Slow and poor healing of wounds

- In hands and feet there is burning tingling sensation due to diabetic neuropathy[19]

Diagnosis:

American Diabetes Association says that any of the following can be used for diagnosis of diabetes:

- HbA1c or glycosylated haemoglobin test
- FPG -a fasting plasma glucose test
- OGTT - an oral glucose tolerance test

The hbA1c levels give an idea about the glucose value during the past 3 months. It gives a fair idea how treatment is working.[18]

The haemoglobin is present inside the red blood cells. The function of haemoglobin is to transport oxygen to the tissues. When the red blood cells are constantly exposed to high level of blood glucose, the glucose enters inside the cells to form a bond with the haemoglobin to form glycosylated haemoglobin. This hba1c gives the average blood glucose control over the past 3 months. Hence it is necessary to check hba1c values at least twice a year.

The A1C test results could be reported as eAG or as "average glucose," which directly correlates with A1C. eAG is a unit similar to self-monitor on the CBG machine. A1C is reported as a percent and eAG as mg/dl .[16]

eAG is not the same average glucose level as the average of values on the meter. This is because people with diabetes more likely check blood glucose when they are low (usually, in the morning and before meals), the average of these readings is mostly lower than eAG.

Fasting Blood Glucose:

It is the blood glucose values which are taken in early morning with fasting for at least 8 hours from previous night.

Oral Glucose Tolerance Test (OGTT):

It's a test to determine how well the body metabolises glucose. Here blood glucose values are taken in fasting. The patient is made to drink a special glucose solution and blood glucose values are taken after 2 hours.

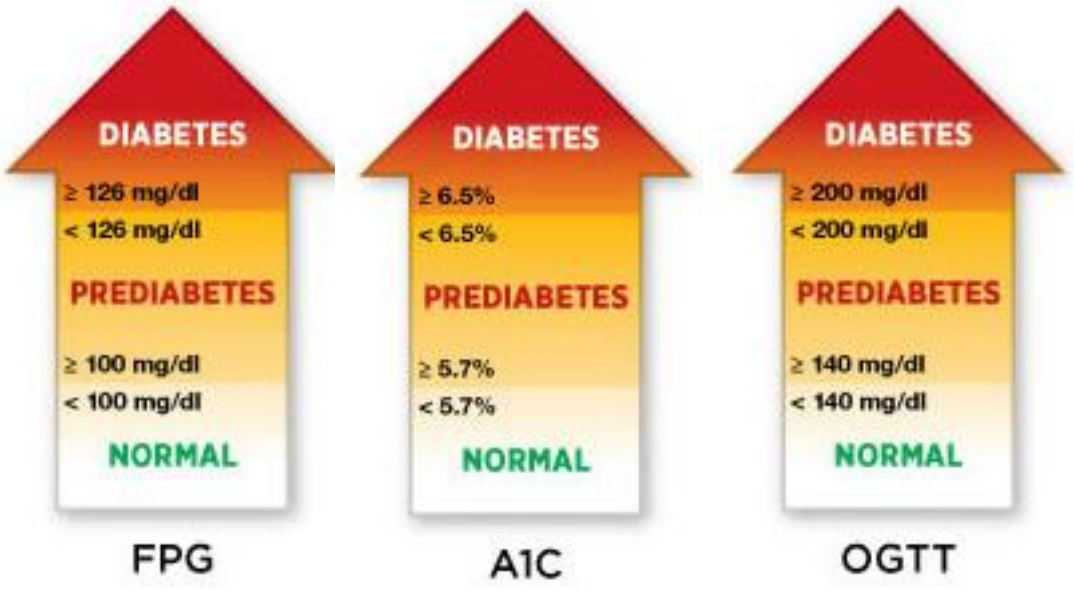
Result	**Oral Glucose Tolerance Test (OGTT)**
Normal	less than 140 mg/dl
Prediabetes	140 mg/dl to 199 mg/dl
Diabetes	200 mg/dl or higher[16]

Random Plasma Glucose Test:

This can be done at any time of the day. When the random plasma glucose values are more than 200mg/dl then it is diagnostic of diabetes

Prediabetes:

Prediabetes is defined as blood glucose levels which are more than normal but not yet high to be diagnosed as diabetes. Both impaired fasting glucose and impaired glucose tolerance come under prediabetes. These people must be regularly followed up for they have a high chance of developing overt diabetes and cardiovascular complications



Complications:

The complications of diabetes are due to the increased blood glucose for a long period of time. It's the duration of diabetes which determines the incidence of complications. The complications due to diabetes can be divided as macrovascular and microvascular. They affect multiple organ system primarily the kidneys, heart, eyes, brain vessels and peripheral vessels of the limbs. It causes diabetic nephropathy, myocardial infarction, cerebrovascular accidents and gangrene of the limbs. Moreover diabetes predisposes to hyperlipidemia and hypertension which increases the risk of complications.

The vascular complications in diabetes mellitus are mainly due to microangiopathy and atherosclerosis. Damage to the endothelial basement membrane, proliferation of endothelial cells and dysfunction of the endothelial cells are mainly responsible for the microangiopathy. Increased blood glucose causes hardening of the vessel wall and this along with increased lipids in the blood results in lipid deposition in atherosclerotic plaques predisposing to end organ damage.

The pathophysiology involved in development of microvascular and macrovascular complications in diabetes is very complex. There is no clear cut mechanism. Increased blood glucose values for a long duration of time have

been found to be the most important single factor causing complications. However not all those who have increased blood glucose develop complications and sometimes even those who have very good control of blood glucose end up developing the complications of diabetes mellitus.

Increased sugar affects many cell types and their extracellular matrix. These changes result in structural and functional alterations in the tissues.

The cell membranes are formed mainly by the phospholipid bilayers. Hence alterations in lipid metabolism affect the cell membranes resulting in damage to the cells. The oxidation of low-density lipoprotein in hyperglycaemic individuals raises oxidant stress in the vessel wall. This attracts the monocytes and macrophages to the vessel wall were oxidized LDL results in alterations in cell adhesion.it also increases the release of cytokines and growth factors. Moreover Growth factor causes multiplication of smooth muscle resulting in increase in thickness of vessel wall. Further there is increased atherosclerotic plaque formation and microthrombi formation in major blood vessel .the changes in vascular permeability and endothelial cell dysfunction causes end organ damage.

Sustained hyperglycaemia causes linking by sugar with proteins, lipids, and nucleic acids. There is increased deposition of advanced glycation end products in the micro blood vessels of the retina, glomerulus, and endoneurons, as well as

the larger blood vessel walls. People who have poorly controlled diabetes mellitus have increased formation of advanced glycation end products. These advanced glycation end products cause change in the structural and functional change in the cells of various tissues. AGE formation on collagen impairs healing of damaged tissues and thus the normal homeostatic process is deranged. AGE-modified collagen forms in the walls of the large blood vessels and causes vessel wall thickening and narrowness of the lumen. These immobilize the circulating LDL, contributing to formation of atherosclerotic plaque. The formation of AGEs causes increase in basement membrane thickening in the retinal microvasculature and around the nerves and increase in thickness of the mesangium in the glomerulus. The end point of all these changes is causing narrowing of the blood vessels resulting in decreased perfusion to the organs.

Formation of AGE has its effect at the cellular level also resulting in changes in extracellular matrix and causing alterations in cell-to-matrix and matrix-to-matrix interrelations. The binding of AGEs to specific cell receptors which have been identified on the surface of smooth-muscle cells, endothelium, neural cells, monocytes, and macrophages causes increased vascular permeability and thrombotic complications, multiplication of smooth muscle in vasculature, and phenotypic changes in monocytes and macrophages. This causes increased responsiveness of monocytes and macrophages on stimulation, which results in

increase in the production of proinflammatory cytokines and associated growth factors. These cytokines and growth factors contribute to the chronic inflammation in the production of atherosclerotic lesions. They also change the wound-healing events. More production of inflammatory mediators causes raised tissue destruction in response to antigens such as the bacteria.

These alterations in protein and lipid metabolism, causes elevated plasma glucose levels which is an important feature of diabetes, which provides a common relation between the different diabetic complications. However, these metabolic changes vary among people. For example, AGEs form in both diabetic and non-diabetic persons, but its accumulation is more in those with diabetes. There are significant differences in AGE formation even within the diabetic population, and it is thought that this may explain the changes in the incidence and progression of diabetic complications.

Management:

The main goal of treatment is to reduce the blood glucose values and keep the values at a level similar to that of normal people and hence to prevent both microvascular as well as macrovascular complications of diabetes mellitus. Other goals are growth and development, normal body mass, avoiding uncontrolled hyperglycaemia or hypoglycaemia, preventing diabetic ketoacidosis and nonketotic acidosis, and immediately detecting and treating

diabetic complications. Diabetics can use glucose meter to monitor the glucose levels closely and ensure that they are within a normal range.

Obesity is a major contributor for development of diabetes. Obesity causes insulin resistance. Hence exercise daily, diet, lifestyle modification and drugs form a corner stage in treatment of diabetes. Type 1 diabetes patients are treated with insulin for survival. Type 2 diabetes patients are treated with oral hypoglycaemic agents however these patients too might require insulin for better control.

Since the publishing of the Diabetes Control and Complications Trial in 1993 there has been great change to the drugs and the goals of therapy for treating diabetes. This prospective randomized controlled clinical trial compared the efficacy of intensive insulin therapy had objectives at achieving normalization of glucose control with the presence of conventional insulin therapy on the start and progress of complications in diabetes. The normal control group took 1 to 2 insulin injections a day whereas the intensive control cohort took 3 to 4 injections daily .During the 9-year follow-up the patients who were intensively treated were found to have much lower complications when compared to the other group.

In those patients who were managed intensively, the risk of retinopathy reduced to 76% in comparison to the normal control group. The Clinical and laboratory

signs and symptoms of nephropathy and neuropathy also reduced by 54%. Macrovascular complications reduced significantly. These results about the benefit of intensive therapy led the American Diabetes Association to issue its protocol for treating type one diabetic patients that they must attain a control of blood glucose values equal to that of the control cohort in DCCT trail.

Even for patients suffering from type 2 diabetes mellitus there is reduction in complications in those patients in whom glucose was intensively managed according to recent studies. In a study, maintenance of normal glycaemia resulted in reduction by 70% the risk of microvascular and macrovascular complications for patients, in comparison to conventional controls. Since more than 90 percent of the patients belong to type 2 diabetes these studies have potential to benefit millions of people worldwide. Hence it's imperative to motivate diabetic patients to have strict sugar control and physicians have intensified diabetic management nowadays.

Treatment - Oral Agents:

An array of oral agents is now available for treatment of patients with type two diabetic mellitus. The first generation sulfonylureas are no longer in use nowadays because of the increased side effects associated with these drugs. Chlorpropamide is an example of first generation sulfonylureas. Second-generation agents which are more potent, have less drug interactions, and produce fewer side effects and hence have replaced the first generation. The

mechanism by which sulfonylureas act is by acting on the pancreatic beta cells and causing increase in insulin secretion. This increased insulin secretion overcomes the resistance associated with type 2 diabetes mellitus and hence more amount of glucose is transported inside the cells thereby decreasing the blood glucose value. The sulfonylureas have duration of action varying from 12 to 24 hours and depending upon that they are given as single or double dosage daily. The major adverse effect associated with sulfonylureas is hypoglycaemia. Hence the patients who take these drugs must be educated properly to take adequate amount of food after taking these tablets.

Repaglinide stimulates pancreatic insulin secretion. But the pharmacodynamic properties and mechanism of action are different from sulfonylureas. Repaglinide undergoes rapid absorption, reaches peak plasma levels in 30 to 60 minutes, and undergoes rapid metabolism. The drug is consumed along with meals and reduces the peaks of PPBS which is common in type 2 diabetes but to a greater degree than the sulfonylureas medications. These drugs are used for the treatment of post prandial hyperglycaemia due to their rapid onset and short duration of action. These drugs can also result in hypoglycaemic episodes.

Metformin are biguanides and are preferred agents for obese patients. These drugs decrease blood glucose by decreasing the production and increasing the utilization. These drugs also inhibit the intestinal absorption of glucose. Lactic acidosis and megaloblastic anaemia due to vitamin b12 deficiency are the major

adverse effects of these drugs. Biguanides increase the intestinal production of lactate by anaerobic glycolysis. Metformin is the only oral agent that has been demonstrated to reduce the macrovascular events in type 2 DM.

The thiazolidinedione group of drugs, which includes troglitazone, rosiglitazone, and pioglitazone, act as agonists of nuclear receptor PPAR gamma which regulates transcription of genes involved in glucose and lipid metabolism. These drugs are used to reverse insulin resistance in type 2 DM. these drugs also tend to increase HDL. The adverse effect of these drugs includes weight gain, edema and plasma volume expansion. Therefore these should be avoided in CHF patients.

Acarbose- complex carbohydrates are absorbed after conversion to simple carbohydrates by alpha glucosidase. Inhibitors of this enzyme decrease carbohydrate absorption for git. Major adverse effect is flatulence due to fermentation of unabsorbed carbohydrates. These drugs help in restoring beta cell function and prevent new cases of type 2 diabetes in pre diabetes

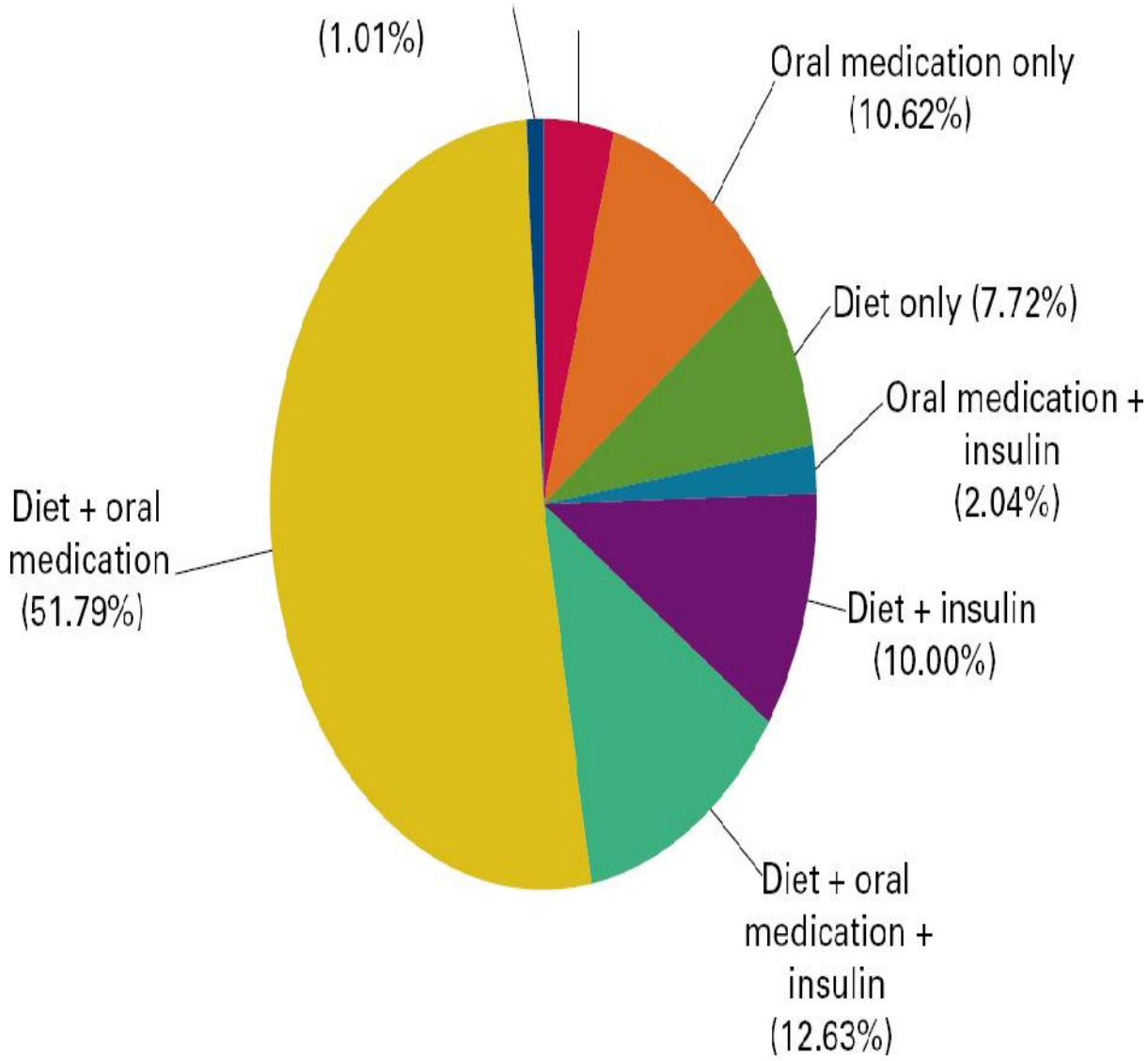


FIG: CHART SHOWING THE DIFFERENT TREATMENTS FOR DIABETES AND ITS EFFICACY

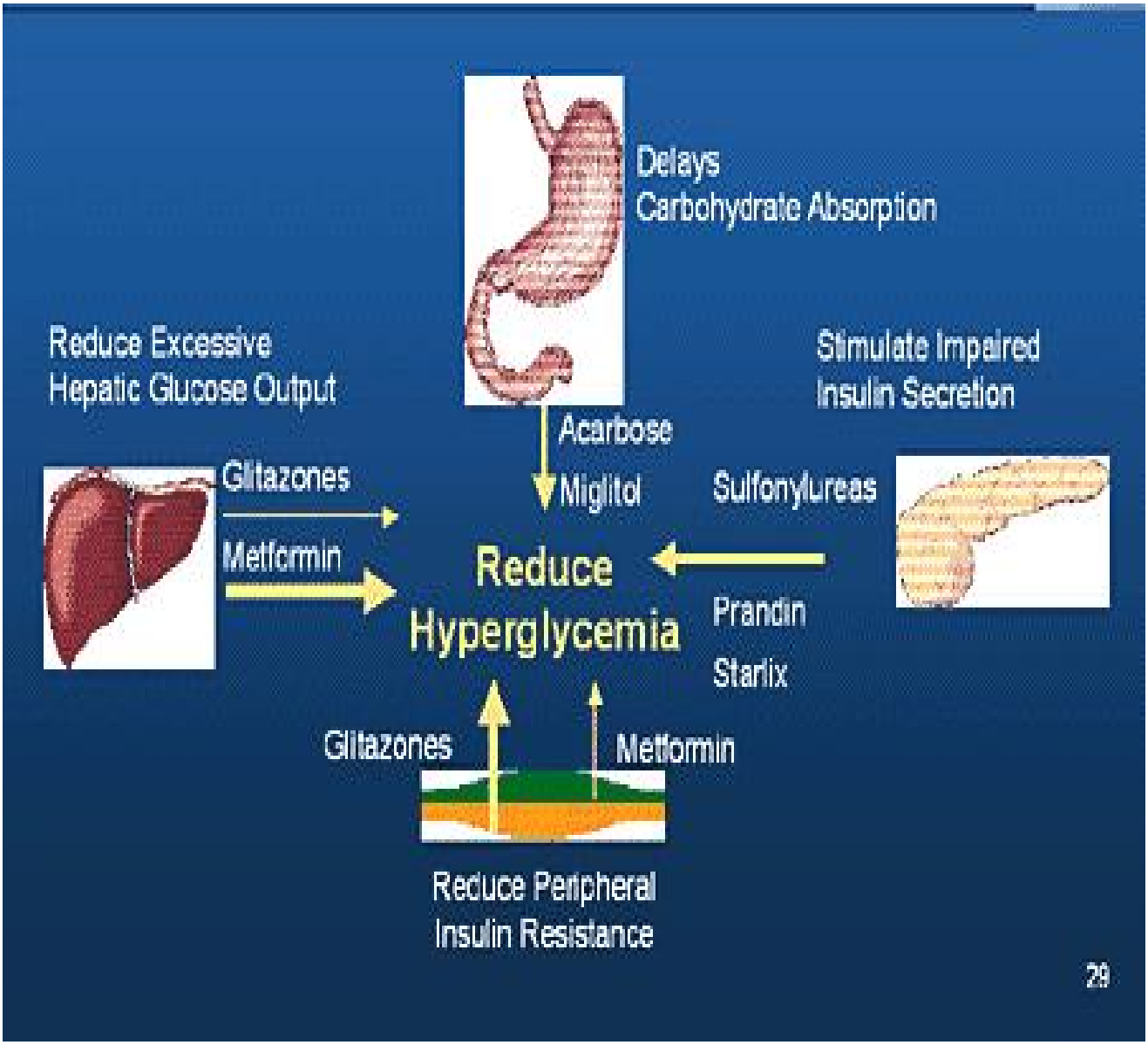


Fig: Diagram showing site of action of anti-diabetic drugs

Table 1 – Non-insulin agents available for treatment of diabetes in the United States

Drug class	Route of administration	Advantages	Disadvantages
Biguanides (metformin)	Oral	Effectively lowers HbA_{1c}, low cost, does not cause weight gain	GI complaints, minimal risk lactic acidosis (contraindica in patients older than 80 y those with elevated creatini
Sulfonylureas (tolbutamide, glyburide, glipizide, glimepiride)	Oral	Available as generics (low cost)	Can cause weight gain
Disaccharidase inhibitors (acarbose, meglitol)	Oral	Do not promote weight gain; safe in patients with renal failure; reinforce carbohydrate restriction through averse response	Flatulence, abdominal disc diarrhea; relatively high co
Thiazolidinediones (rosiglitazone, pioglitazone)	Oral	May preserve beta cells from ongoing destruction	Cause fluid retention (somet leading to heart failure); sti accumulation of adipose tis
Meglitinides (repaglinide, nateglinide)	Oral	Rapid disappearance time results in lower risk of hypoglycemia than with sulfonylureas	Much shorter duration of ac sulfonylureas; thus, these ag be taken before meals; mo high cost
GLP analogs (exenatide)	Parenteral	May result in progressive weight loss in some patients	Nausea (often severe); must injected twice daily; high c
Amylin analogs (pramlintide)	Parenteral	Weight loss can occur	Nausea; unpredictable hyp high cost
DPP-IV inhibitors (sitagliptin)	Oral	No prominent side effects, low risk of hypoglycemia	Does not lead to weight los

HbA_{1c}, glycosylated hemoglobin; GLP, glucagonlike peptide; DPP-IV, dipeptidyl peptidase IV

Insulin:

Insulin was discovered by Banting and Best in the year 1921. Glucose is the main stimulus for the release of insulin from the beta cells of the pancreas. Glucose stimulates GLUT-2 and inhibits ATP sensitive k+ channels. The actions of insulin include stimulation of entry of glucose in muscle and fat, inhibition of glycogenolysis and gluconeogenesis and increasing glycolysis and glycogenesis. By all the above mentioned mechanisms insulin decreases the blood glucose levels. It also inhibits lipolysis and favours deposition of triglyceride. It caused increased synthesis of proteins and thus overall has an anabolic action.

The human insulin is prepared by recombinant DNA technology and has rapid absorption and shorter duration of action. Recently ultra-short acting and ultra-long acting preparations have also been developed. All insulin preparations are supplied at neutral pH of 7.2 to 7.4 except glargine which is supplied at pH of 4. Hence it is important that glargine should not be mixed with any other preparation of insulin.

All insulin preparations are given by subcutaneous route only. Only regular insulin can be given by intra venous route. The factors which affect the absorption of insulin include the type and site of injection, the depth of injection and subcutaneous blood flow.

The most common complication of an insulin therapy is hypoglycaemia. This can be treated with intravenous glucose. Some people suffer from hypoglycaemic unawareness. Usually when the blood glucose levels drop less than 60mg/dl the symptoms of hypoglycaemia becomes apparent. However in patients suffering from hypoglycaemic unawareness there is no symptoms till blood glucose values plummets to 40mg/dl. The patient becomes unconscious and often this condition is life threatening. Then at the site of injection it can cause lipodystrophy. Allergic reactions and sodium and water retention have found to occur.

The indications of insulin therapy include all cases of insulin dependent diabetes mellitus. Among non insulin dependent diabetes mellitus insulin is indicated when glucose levels are not controlled with oral hypoglycaemic agents, in pregnancy and in complications like diabetic ketoacidosis and hyperosmolar coma in in stressful conditions like surgery and infections.

The use of exogenous insulin provides a profile similar to the non-diabetic individual, with a continuous availability of insulin available which is enhanced by increase in availability after each meal. No single insulin preparation is available which are able to achieve this goal with one or two injections daily. Insulin preparation combinations are available which are taken three or more times daily or using a subcutaneous infusion pump more approximate to the

ideal conditions, but even in conditional regimes, blood glucose levels can remain unstable.

Ultralente insulin also called as "peakless" insulin is the longest acting insulin.it has a very slow action onset of action and it peaks very minimum and action is for a longer duration. It action resembles the basal metabolic insulin which is secreted from a normally functioning pancreas. The intermediate-acting insulin (lente and neutral protamine Hagedorn [NPH]) have their peak action several hours after injection. Peak activity occurs between 4 to 10 hours after injection. Therefore a patient who is using intermediate-acting insulin in the early morning will have peak plasma insulin levels during lunch hours. Regular insulin is shorter acting, with its onset being around about 30 minutes through 1 hour post injection and peaks at 2 -3 hours. Lispro insulin, a rapid acting insulin, due to its rapid absorption, will become active about 15 minutes post injection, and peaks at ½ to 11/2 hours. Rapid- and short-acting insulin are usually taken just before or during meals. Thus, regular insulin when taken before breakfast will peak at midmorning; when taken before lunch, will peak at mid-afternoon.

Insulin preparation	Onset of action	Peak	Duration of action
Lispro (Humalog)	<15 minutes	1-2 hours	3-6 hours
Aspart (Novolog)	<15 minutes	1-2 hours	3-6 hours
Glulisine (Apidra)	<15 minutes	1-2 hours	3-6 hours
Regular (Novolin R, Humulin R)	30-60 minutes	2-4 hours	6-10 hours
Humulin R Regular U-500	30-60 minu tes	2-4 hours	Up to 24 hours
NPH (Novolin N, Humulin N, ReliOn)	2-4 hours	4-8 hours	10-18 hours
Glargine (Lantus)	1-2 hours	Usually no peak	Up to 24 hours
Detemir (Levemir)	1-2 hours	Usually no peak**	Up to 24 hours**

Premixed Insulins***	Onset of action	Peak	Duration of action
Novolin70/30, Humulin 70/30	30-60 minutes	2-10 hours	10-18 hours
Humalog 75/25, Novolog 70/30, Humalog 50/50	10-30 minutes	1-6 hours	10-24 hours

Prevention:

Daily regular exercise, healthy food habits, having an apt weight plays a major role in preventing diabetes and the complications. These also help in reducing the blood pressure and heart disease among type 2 diabetic patients.

DIABETES AND THYROID

In liver, skeletal muscle and adipose tissue the thyroid hormones have different modes of action and hence these are the main targets of action. Their action is opposite to that of insulin and increases gluconeogenesis and glycogenolysis in the liver.[61, 62]

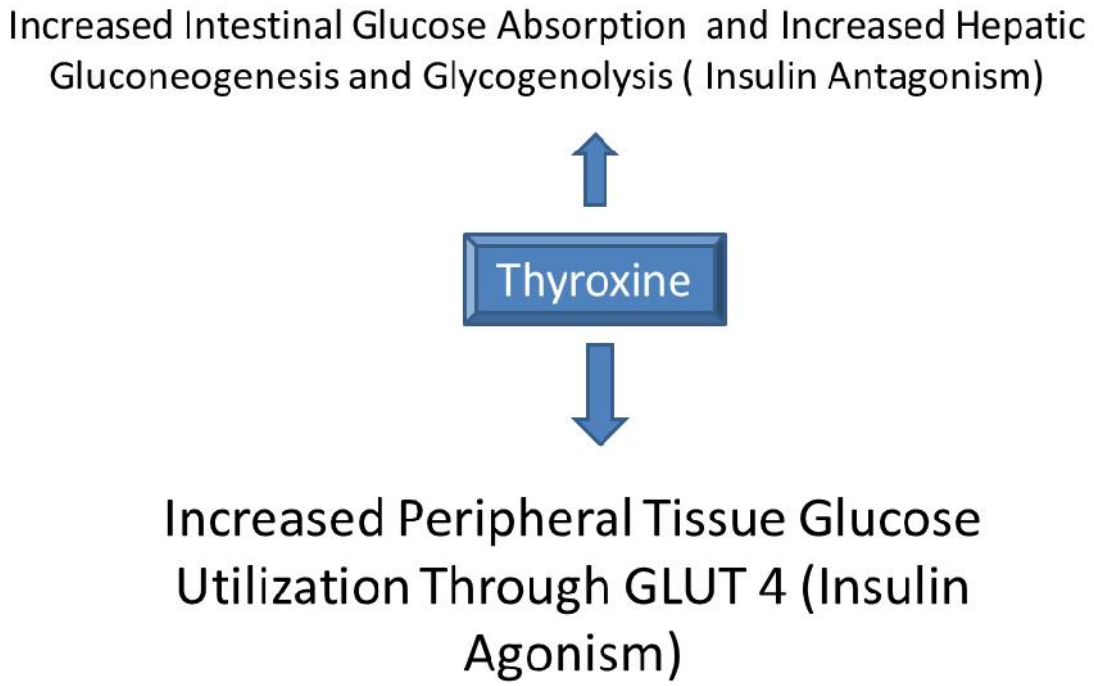
They act by up-regulating the expression of GLUT-4 and phosphoglycerate kinase genes, thus facilitating their action along with insulin[63, 64] and improving the disposal and utilisation of sugar in tissues.[60, 65]

Thyroid disease in the general population: 6.6%
Thyroid disease in diabetes: Overall prevalence: 10.813.4%
Hypothyroidism: 36%
Subclinical hypothyroidism: 5-13%
Hyperthyroidism: 12%
Postpartum thyroiditis: 11%

There is a strong association between thyroid disease and type-2 diabetes, and there are vital consequences for it on insulin sensitivity and treatment. The basis

of this association pathophysiologically has been better described recently. The basis is a complex interplay of major signal paths and associated genetic susceptibility. The mechanisms which underlie this linked process are being studied more. The explanation to this regulation is by 5' adenosine monophosphate-activated protein kinase (AMPK) which regulates the insulin sensitivity and also the thyroid hormone feedback.[5] There are many significant citings that have shown a more than normal prevalence of thyroid disorders in type 2 diabetic patients, with hypothyroidism especially subclinical hypothyroidism which is the most commonly associated with diabetes.[3,4,39]

The figure below shows the relation of diabetes and thyroid normally:



There are few studies that suggests genetic basis between thyroid disease and type two diabetes (unlike type-1 diabetes) [54]. Recently data have been produced

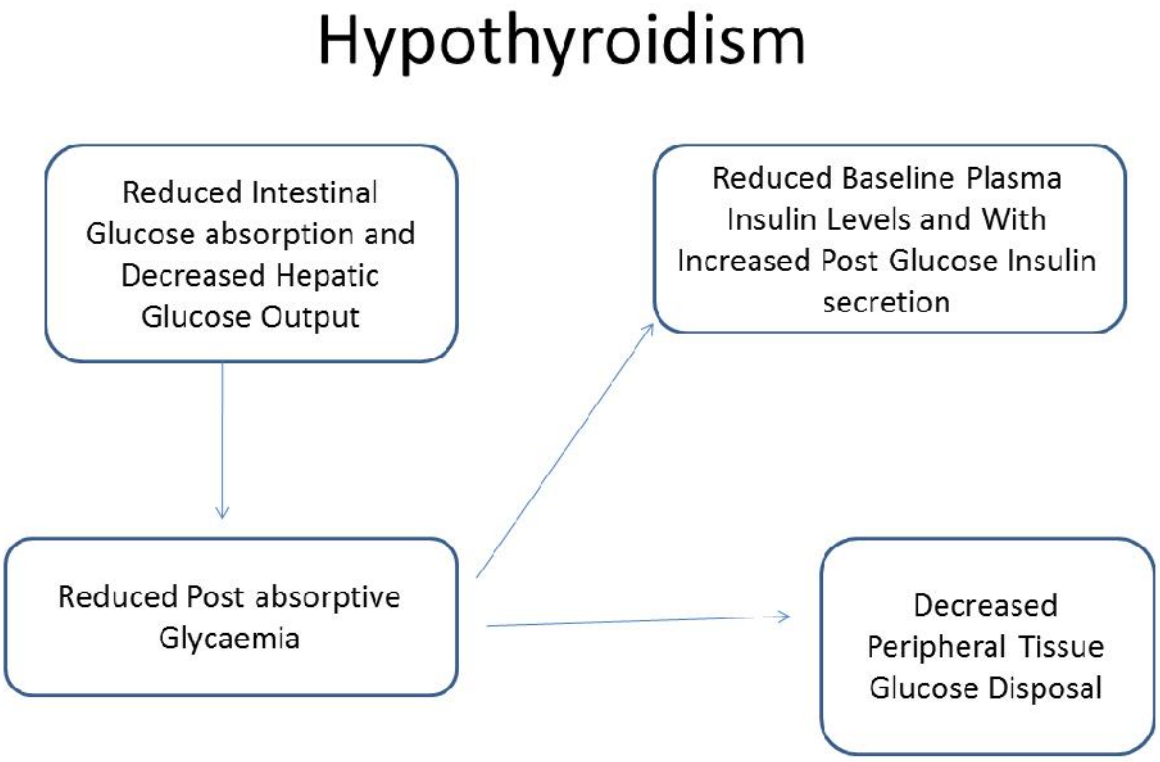
showing association between de-iodinase 2 gene, Thr92Ala, and increased development of type diabetes mellitus. This was strongly supported by a meta-analysis of 11,000 people showing the place of intracellular T3 on sensitivity of insulin.

Carbohydrate metabolism have shown many changes in hypothyroidism, signs and symptoms of which are not conspicuous. But the insulin degradation decreases the requirement for exogenous insulin. In presence of hypoglycaemia in isolated hypothyroidism (clinical/subclinical) the probability of hypopituitarism in a hypothyroid patient should be suspected. More notably, many lipid metabolism abnormalities are associated with hypothyroidism, such as increased triglycerides and LDL cholesterol. Coexisting dyslipidaemia in subclinical hypothyroidism may increase and this is commonly associated type-2 diabetes and raises the risk for cardiovascular diseases. Thyroxine replacement if adequate will normalise the lipid abnormalities and bring it back to normal. Diabetic kidney injury which is severe can be thought of as hypothyroidism because both categories of patients can have swelling of body and legs, weakness, anaemia, and gain of weight.

Poorly controlled diabetes further complicates the diagnosis of hypothyroidism that can produce changes in thyroid function tests which can happen in absence of thyroidal illness too. The alterations typically include a reduced T3 due to

changes in extrathyroidal T4 to T3 conversion, a decreased level of T4 due to decrease in protein binding, and associated low levels of TSH in blood.

The short term and long term interaction of thyroid hormones on glucose and lipid metabolism with regulation of energy web and through its direct relation with insulin regulation and glucose utilisation in peripheral tissues it regulates the metabolic process in the body.



Glucose and Lipid Metabolism regulation by Thyroid hormones:

Recently published data suggest a vital role for regulation by hypothalamus of lipid and sugar control.[22,37] Human data showed defects in counter-regulating glucagon and the sympathetic portion of the autonomic system of nerves with

hypothalamic versus defects in pituitary , which indicates the vital role of hypothalamic glucose sensing system.[38] AMPK is a conserved cellular energy sensor which controls cell metabolism, and nutritional and hormonal support maintenance in the body.[39] AMPK knockout in related POMC or agouti-related protein-expressing neurons lead to changes in energy control. The mice which knocked out of the gene and used for AMPKα2-regulated POMC were fat as a consequence of reduced use of energy and feeding which was irregularised. Their response to leptin and insulin was good but the sensing of extracellular sugar levels was impaired. On the contrary, AMPK2α KO in AgRP nerve cells remained thin and was showing increased sensing of melanocortin.[37] The control of metabolism by hypothalamus through AMPK been discovered in very close times. Glucose production in peripheral tissues can be reduced by AMPK inhibition.[39]AMPK regulates in sugar utilisation through fatty acid synthesis by the catalytic reaction regulated by acetyl coA carboxylase which is used to convert acetyl CoA to malonyl CoA. This said reaction which is the rate limiting step of fatty acid synthesis is controlled by AMPK phosphorylation and this results in the formation of malonyl-CoA, and this results in elongation of fatty acid chains which is catalysed by fatty acid synthase .[40] Malonyl-CoA also suppresses fatty acid oxidation by controlling the translocation of fatty acids into the mitochondria, a reaction catalysed by carnitine palmitoyl transferase-1 [41]. Glucose control and regulated food intake can be achieved by keeping this pathway as a target in obesity and for decreasing lipid oxidation by

hypothalamus.[41] Thyroid hormones control the above two important regulatory steps in a direct manner.[29]Peripherally, AMPK is dependently stimulated by T3 in terms of dose and time.[42] CPT-1 and mitochondriogenesis is stimulated by T3 and T3 mimetics though its action on CPT-1.[43] This increases the probability that direct targets of thyroid hormones include CPT-1 and AMPK, which has recently been confirmed experimentally in animals .[22] Hypothyroid animals have been evaluated and showed a rise in concentration of AMPKα1 and role on hypothalamus but not muscle or fat. Activity of AMPK reduced when T3 was injected over long periods intracerebrally at a dose which does not have the capacity of rising T3 levels in peripheral tissues. More evidence addition was produced when AMPKα inhibition was achieved by stereotactic injection of a negative variety of AMPK into hypothalamus's ventromedial segment in rats which were euthyroid. Weight loss in phenotypic variety of rats was independent of feeding. Energy-regulating neuropeptides in the hypothalamus had a controlled expression, but beta adrenergic stimulation of the brown fat was characteristically raised.CPT1 was associated changes in AMPK; this associates thyroid hormone related control with energy regulation proteins which act peripherally such as ghrelin that makes AMPK/CPT1 regulatory system in the hypothalamus as the main target. Energy maintenance and hypoglycaemia's counter regulation are controlled by the effect of ghrelin in the body and thus shows its vitality.

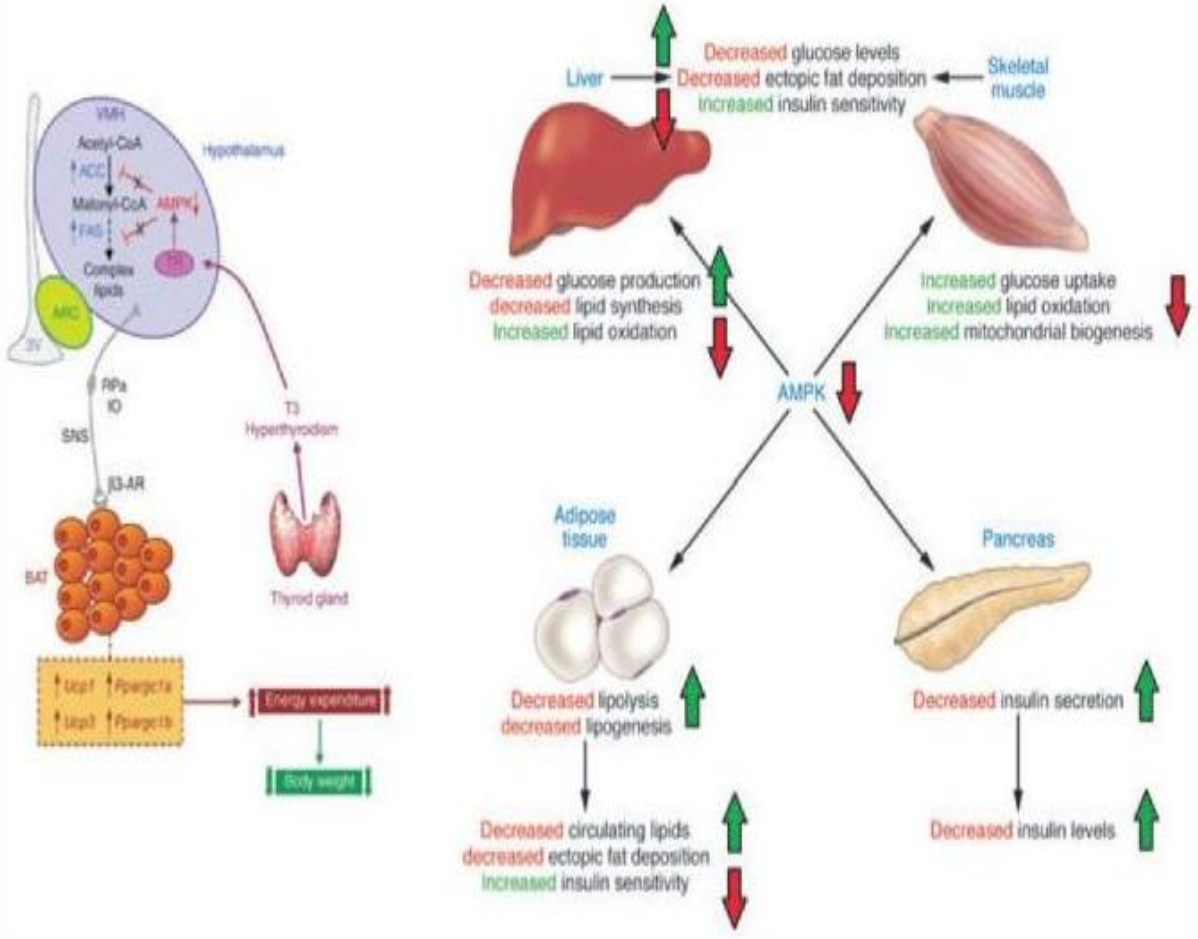


Fig: Regulation of AMPK by thyroid hormones

Thyroid Hormones, Ghrelin and Adipokine Regulation:

Different effects of thyroid hormones have been reported on adipokine regulation, in particular leptin. TNFα which is raised in decreased thyroid function is showing that the major adipokines which is associated with insulin resistance reduces the disposal of glucose and rise in fatty acids[47]. An increase in IL-6is more linked to insulin resistance and is the primary marker and the above said association is only secondary to the relation between diabetes and hypothyroidism.[47]

Effects of Thyroid Hormones on Insulin Secretion and Sensitivity in peripheral tissues:

The effect of thyroid hormones, T4 and T3, on body homeostatic energy and metabolic regulation is explained by its action on peripheral tissues. Secretion of insulin is influenced by thyroid hormone. Hypothyroidism caused decrease in glucose-related beta cell insulin secretion. Gene array studies in hypothyroid patient's skeletal muscle have shown a classical effect on sugar transporter expression by down regulating the GLUT5 in hypothyroidism. On the contrary, expression of GLUT4 is not changed, but model animals showed altered translocation of GLUT4 to the cell membrane and negative alteration of enzyme based degradation of intracellular sugar in decreased thyroid function's presence[20]. The oxidation of glucose and synthesis of glycogen are reduced in decreased thyroid function. The sensitivity of insulin is improved parallely with

rising thyroid hormone concentrations. This is dependent on production of T3 within the cells as polymorphisms of de-iodinase with reduced generation of T3 have a close association with resistance of insulin in diabetic patients.

Thyroid Hormone and Insulin Resistance:

A positive association between insulin resistance and thyroxine is not only diabetic patients but also in people with normal sugar tolerance. Insulin resistance indices as evaluated by the homeostatic model assessment (HOMA, which judges before meal and post meal resistance of insulin) are related to normally functioning thyroid subjects, where HOMA is associated with an increase in thyroid concentrations normally.

The interaction between thyroid status and metabolic control shows the requirement for keen monitoring of thyroid function in type 2 diabetes mellitus patients. As proved through studies that thyroid dysfunction prevalence in T2DM is similar to T1DM, it is necessary to put forth new recommendations for frequently investigation, on yearly or twice yearly basis, in groups which are of greater risk like patients over 50 or 55 years, especially in presence of clinical, increased titres of antibody or lipid abnormalities. So it is necessary to suggest that an initial testing of TSH and TPO antibody that helps to analyse the development of hypothyroidism in patients with diabetes mellitus.

Indications for Treatment of Persistent Subclinical Hypothyroidism[7]
Postmenopausal osteoporosis Rheumatic valvular disease with left atrial enlargement or atrial fibrillation Recent-onset atrial fibrillation or recurrent cardiac arrhythmias Congestive heart failure Angina pectoris Infertility or menstrual disorders Nonspecific symptoms such as fatigue, nervousness, depression, or gastrointestinal disorders, especially in patients older than 60 years of age (consider therapeutic trial)

Diet for Diabetes with Hypothyroidism:

A food combination for diabetes with hypothyroidism requires specific details. Intake of certain foods with hypothyroidism or diabetes causes symptoms to exacerbate. Knowledge of what to eat, and when, help in managing blood glucose levels and thyroid hormone levels. Hypothyroidism commonly causes weight to increase, which further deteriorates the blood sugar control. A diet for both illnesses should certainly address weight, food reactions, and blood sugar levels (glycaemic index).

What to Eat:

A healthy diet which is full of nutrient-dense foods and which has less of carbohydrates is the most important combination for diabetes and hypothyroidism. Vegetables and lean protein must consist of in the bulk of the food. Fish, chicken breast, and lean beef are useful to be included in the diet. Pork and turkey breast are accepted as forms of lean protein. Intake of eggs, cheese, and yoghurt are important and not contraindicated. Vegetarians should replace lean meat with beans and nuts as their protein source. There should moderation while eating fruits because of their different effects on blood sugar levels. Fruits which have lower glucose spikes should be taken. Berries are useful. Drinking lots of water helps a lot.

When to Eat:

When to eat is very critical and is as important as what to eat in diabetes with hypothyroidism. Skipping breakfast is harmful as it is the precursor of metabolism. We should take smaller meals which are spread through the entire day and not rely on two or three large meals. The biggest meals should be early, and supper should be light. Healthy foods should be used as snacks when hunger sets in. Dinner should be the last meal. Lean protein snacks should be taken as snacks.

Foods to Avoid:

High-carbohydrate foods should not be taken, and when consumed, the portion sizes should be in the right manner. Cruciferous vegetables are an important alternative (such as broccoli) in moderation as they cause interference with thyroid gland functioning. Soy also alters the thyroid gland function and prevents the efficacy of thyroid replacement medicines. There should be fewer intakes of saturated fats, like fatty meats, and they should be replaced with healthy fats, such as omega3 fatty acids, which are associated with foods like fish and flax. Soda and other sugary drinks should be avoided from diet. Food allergy test should be done to show any specific foods to avoid. Food allergies are sometimes associated with other autoimmune diseases like hypothyroidism due to similar etiologies.

Weight Loss:

Maintenance of a healthy weight for better blood sugar control plays a vital role, but this becomes more difficult in conjunction with hypothyroidism. Losing weight becomes next to impossible. Metabolism will be slower and the body cannot function as it should normally. Exercise should be put into the daily schedule of the patient for better control of weight and sugar levels. The ADA recommends that at least 30 minutes a day should be spent in exercise. Sleep also plays a vital role. When sleep is not enough the body will have a cortisol imbalance, which results in feeling hungry even after consumption of

food. Decreased sleep will also affect the body's ability for carbohydrate break down, and this result in a raise in blood sugar. Sleep deprivation should be prevented.

III. AIMS AND OBJECTIVES

The main objectives of the study are as follows:

1. To study the prevalence of Hypothyroidism (Clinical/Subclinical) in Diabetic patients
2. To study the correlation of HbA1c levels with TSH levels

IV. MATERIALS AND METHODS

PLACE OF STUDY

Stanley Medical College and Hospital, Chennai:

Department of General Medicine, Endocrinology OPD, Medical wards

SAMPLE SIZE: 50

DURATION

February 2014 - September 2014.

STUDY DESIGN

Prospective Observational Study

ETHICAL COMMITTEE APPROVAL

Ethical committee approval was obtained for the study

PATIENT SELECTION

Inclusion Criteria:

1. Any patient coming with history of type 2 Diabetes Mellitus of more than 3 years duration with or without Hypothyroidism.
2. Any patient on treatment for Hypothyroidism with history of type 2 Diabetes.

Exclusion Criteria:

1. Patients with type 2 Diabetes Mellitus for less than 3 years duration.
2. Patients in Hyperglycaemic emergencies.
3. Patients with pervious history of Thyroid surgery.

METHODOLOGY

Patients coming with history of type 2 diabetes mellitus with or without history hypothyroidism of more than 3 years duration or patients on treatment for hypothyroidism with history of diabetes mellitus presenting to OPDs or admitted in wards from February 2014 to September 2014 are included in the study. Patients are subjected to symptom analysis, clinical examination, blood investigations including HBA1C and TSH levels. The newly diagnosed patients of hypothyroidism in diabetes were treated with thyroxine for three months and followed up with TSH and HBa1c levels. The final analysis will be made at the end of the study to achieve the aforementioned goals.

CONSENT

The study group thus identified by the above criteria (inclusion and exclusion criteria) was first instructed about the nature of the study. Willing participants were taken up for this study after getting a written / informed consent from these patients or their relatives in the local vernacular language.

STUDY SUBJECTS

All the patients who fulfilled the inclusion criteria above 30 years of age and both genders were included in this study. The included patients were subjected to detailed history taking, complete physical examination and the relevant laboratory investigations as per a proforma, exclusively designed for the study.

The details of the thyroid problem and diabetes mellitus were obtained from the patients and attenders and scrutinising their old records closely.

V. RESULTS AND DISCUSSION

GROUP DISTRIBUTION

Treatment Groups	Name of Group	Study	Number of Subjects
Group A	Euthyroid	To assess the prevalence of hypothyroidismin diabetes mellitus	45
Group B	Hypothyroid		5

STATISTICS

Descriptive statistics was done for all data and suitable statistical tests of comparison were done. Continuous variables were analysed with the Unpaired t test and categorical variables were analysed with the Chi-Square Test and Fisher Exact Test. Statistical significance was taken as $P < 0.05$. The data was analysed using EpiInfo software (7.1.0.6 version; Center for disease control, USA) and Microsoft Excel 2010.

SAMPLE SIZE CALCULATION

Sample size was determined on the basis of a pilot study in which the prevalence of hypothyroidism in diabetes mellitus was measured at 15%. We calculated a minimum sample size of 48 patients was required in each group, assuming a type 1 error (two-tailed) of 0.05 and a margin of error of 10%. Therefore, the final sample selected was n= 50.

$$n = \frac{t^2 \times p(1-p)}{m^2}$$

Description:

n = required sample size
t = confidence level at 95% (standard value of 1.96)
p = estimated prevalence of malnutrition in the project area (15%)
m = margin of error at 10% (standard value of 0.05)

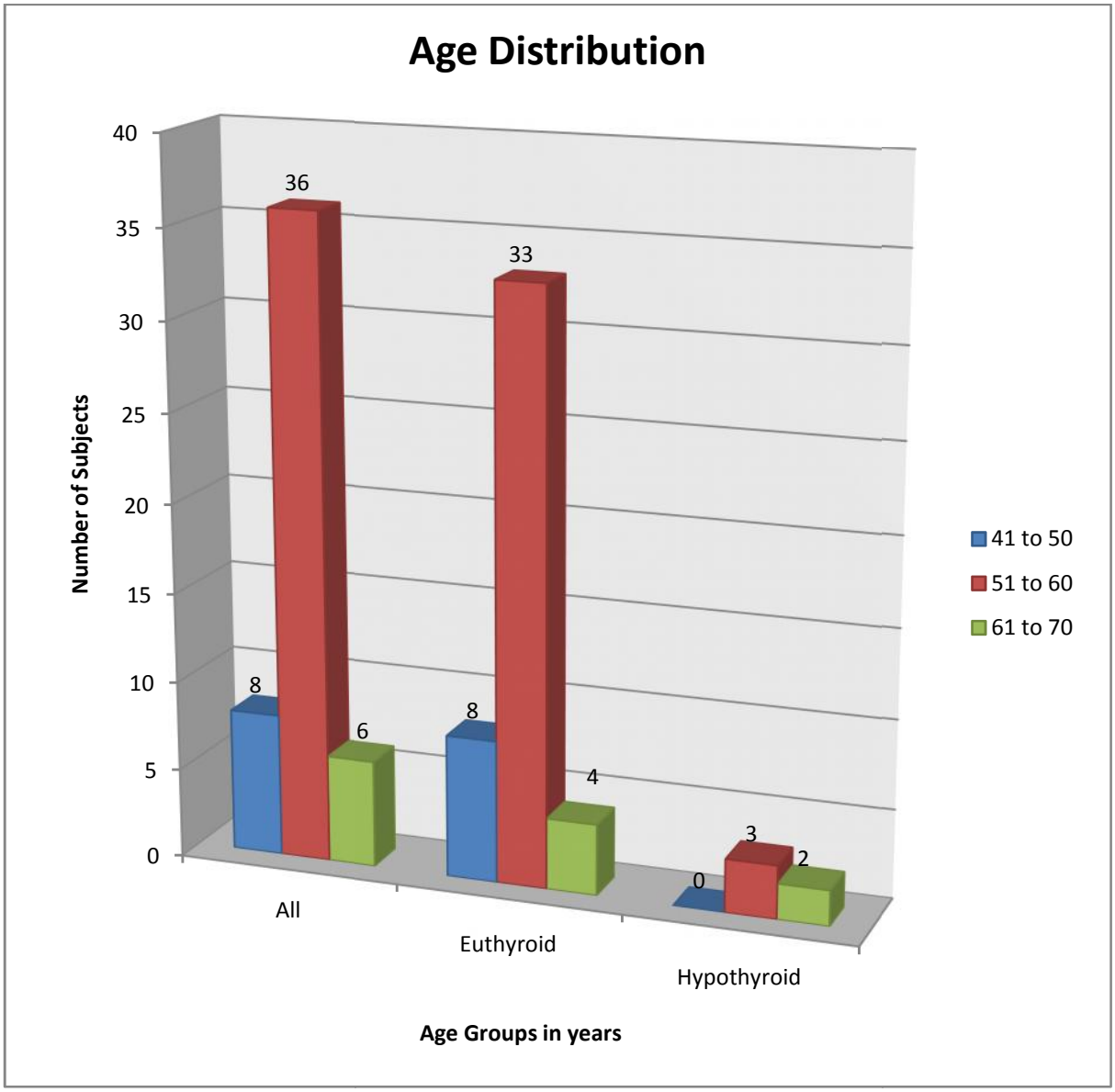
$$n = \frac{(1.96)^2 \times 0.15(1 - 0.15)}{(0.01)^2}$$

$$n = \frac{3.8146 \times 0.1275}{0.0001}$$

$$= 49$$

AGE DISTRIBUTION

Data:



Discussion:

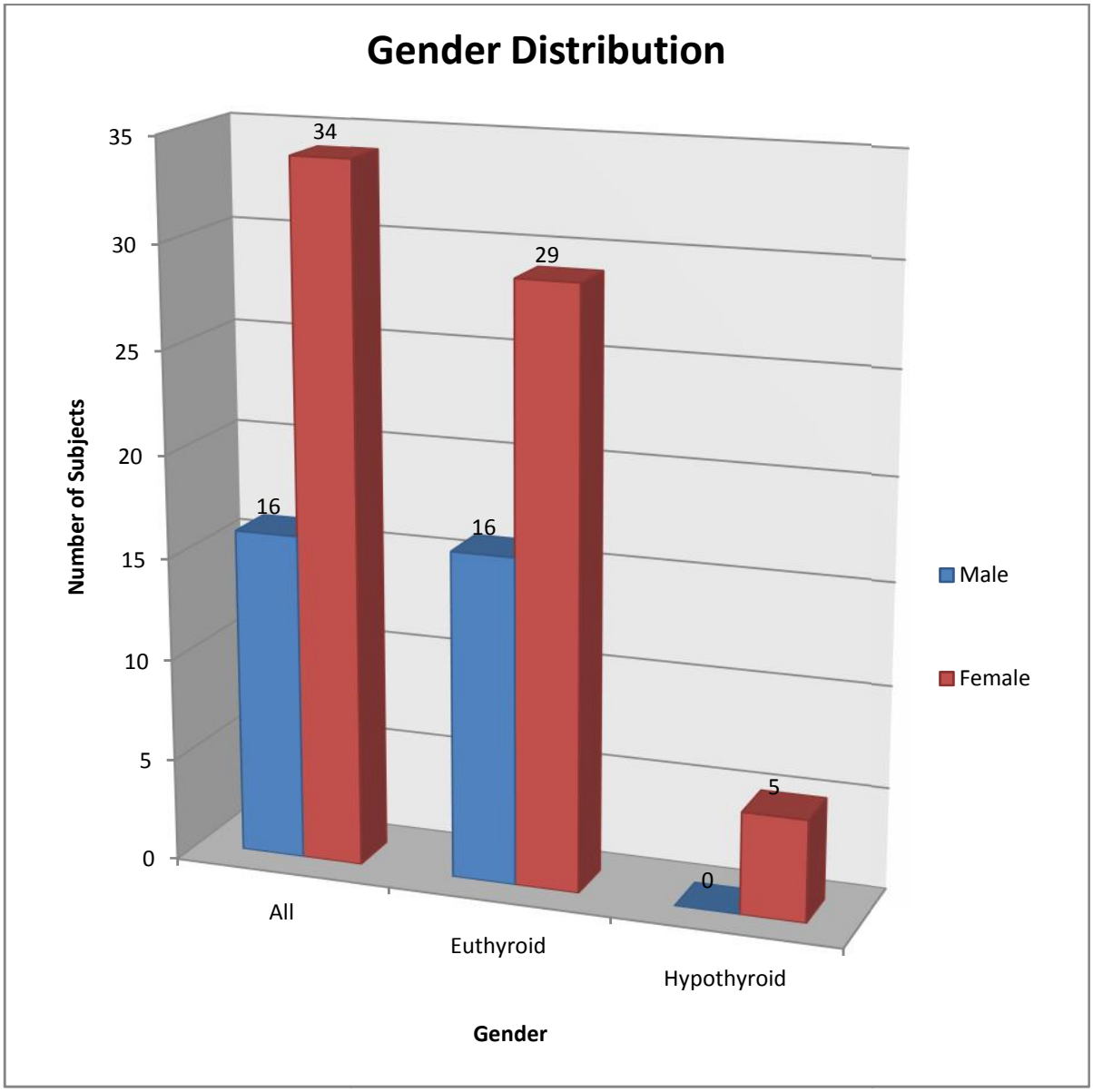
Age Distribution	All	%	Euthyroid	%	Hypothyroid	%
41 to 50	8	16	8	17.77778	0	0
51 to 60	36	72	33	73.33333	3	60
61 to 70	6	12	4	8.888889	2	40
Total	50	100	45	100	5	100

Age Distribution	Euthyroid	Hypothyroid
N	45	5
Mean	55.27	59.00
SD	4.43	6.75
P value Unpaired t test	0.2877207	

By conventional criteria the association between the study groups and age is considered to be not statistically significant since $p > 0.05$.

GENDER

Data:


Gender Distribution
35
30
25
20
15
10
5
0
Number of Subjects
34
29
16
16
5
0
All
Euthyroid
Hypothyroid
Gender
Male
Female

Discussion:

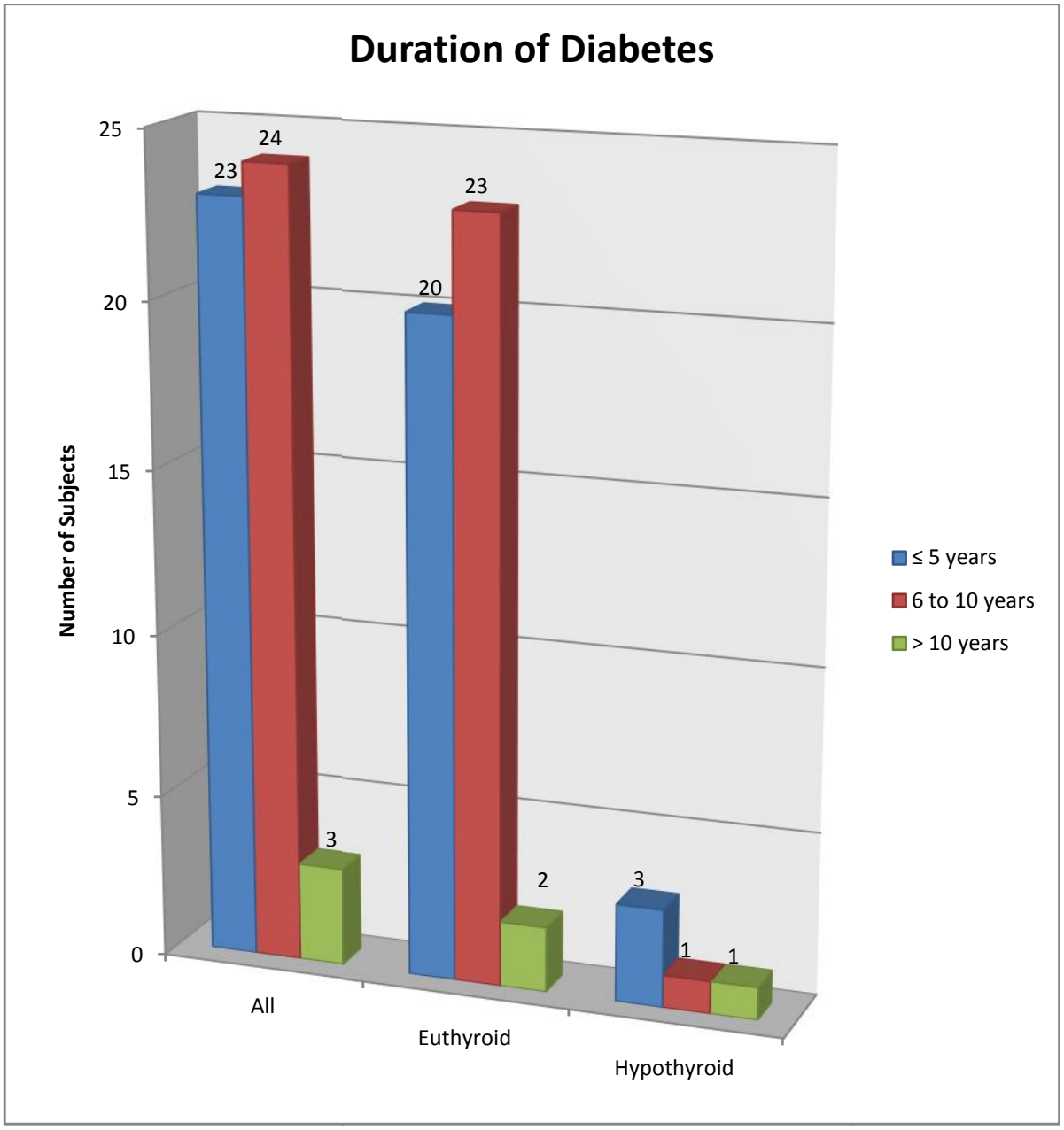
Gender Distribution	All	%	Euthyroid	%	Hypothyroid	%
Male	16	32	16	35.56	0	0
Female	34	68	29	64.44	5	100
Total	50	100	45	100	5	100
Chi-square statistic	2.61					
Degrees of freedom	1					
P value Chi squared Test without Yates Correction	0.106					

By conventional criteria the association between the study groups and gender is considered to be not statistically significant since $p > 0.05$.

Since age and gender is not statistically significant, it means that there is no difference between the groups. In other words the groups contain subjects with the same basic demographic characteristics.

DURATION OF DIABETES

Data:



Discussion:

Duration of DM	All	%	Euthyroid	%	Hypothyroid	%
≤ 5 years	23	46	20	44.44	3	60
6 to 10 years	24	48	23	51.11	1	20
> 10 years	3	6	2	4.44	1	20
Total	50	100	45	100	5	100

Duration of DM	Euthyroid	Hypothyroid
N	45	5
Mean	6.00	7.60
SD	2.08	3.71
P value Unpaired t test	0.03940563*	

By conventional criteria the association between duration of diabetes and hypothyroidism is considered to be statistically significant since $p < 0.05$.

Statistical Significance:

This indicates that there is a true difference among the study groups and the difference is significant.

In simple terms, while assessing the prevalence of hypothyroidism in in diabetes mellitus, the average duration of diabetes mellitus is 6 years in euthyroid

patients compared with 7.6 years in hypothyroid patients with a p-value of 0.03940563 according to Chi-Squared test.

Clinical Significance:

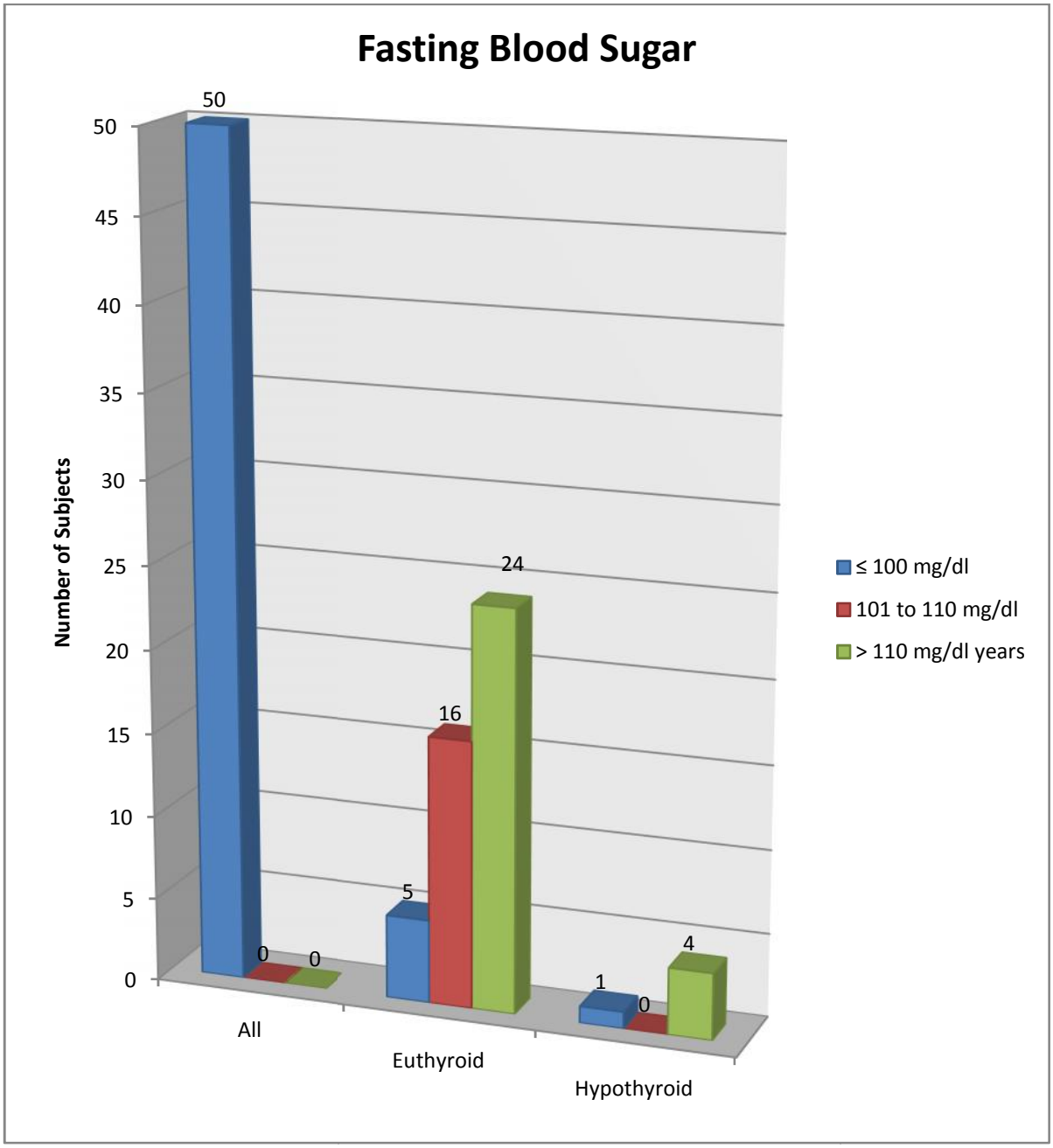
The duration of diabetes mellitus is meaningfully less (26.66%) in euthyroid compared to hypothyroid patients by a difference of 1 year and 7 months. Also the incidence of hypothyroid state in diabetic patients is much more in the first five years of diabetes mellitus (60%). This difference is true and significant and has not occurred by chance.

Conclusion:

We conclude that there is an increased frequency of hypothyroidism early in duration of diabetes mellitus. This also proves that diabetes mellitus patients are at risk of developing hypothyroidism as a complication more in the first five years in our study.

FASTING BLOOD SUGAR

Data:



Discussion:

Fasting Blood Sugar	All	%	Euthyroid	%	Hypothyroid	%
≤ 100 mg/dl	50	100	5	11.11	1	20
101 to 110 mg/dl	0	0	16	35.56	0	0
> 110 mg/dl years	0	0	24	53.33	4	80
Total	50	100	45	100	5	100

Fasting Blood Sugar	Euthyroid	Hypothyroid
N	45	5
Mean	111.98	119.00
SD	8.91	13.08
P value Unpaired t test	0.008211*	

By conventional criteria the association between fasting blood sugar and hypothyroidism is considered to be statistically significant since $p < 0.05$.

Statistical Significance:

This indicates that there is a true difference among the study groups and the difference is significant.

In simple terms, while assessing the prevalence of hypothyroidism in diabetes mellitus, the average fasting blood sugar is 111.98 mg/dl in euthyroid patients

compared with 119 mg/dl in hypothyroid patients with a p-value of 0.008211 according to Chi-Squared test.

Clinical Significance:

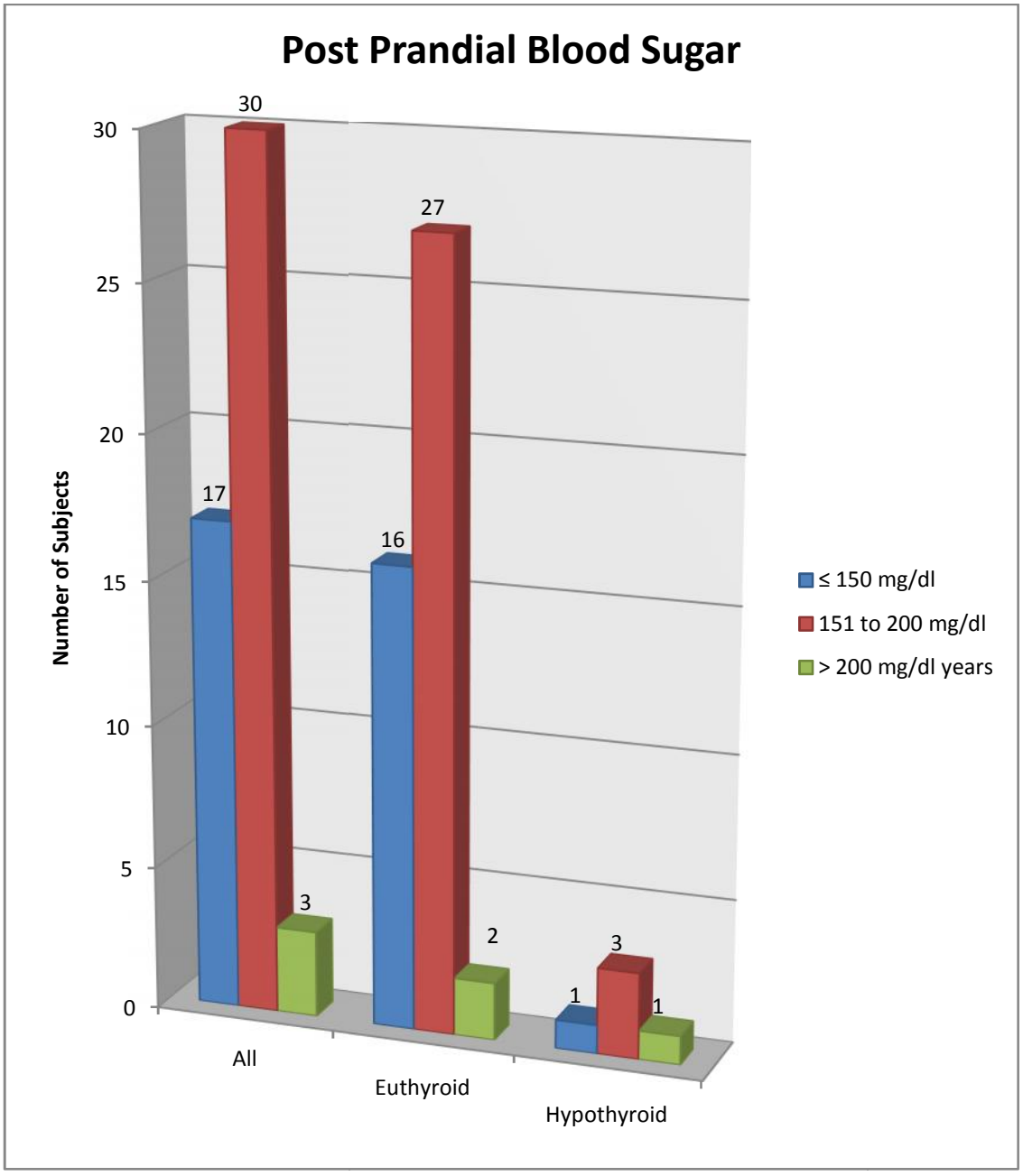
The average fasting blood sugar is meaningfully less (6.27%) in euthyroid patients compared to hypothyroid patients by a difference of 7.02 mg/dl. This difference is true and significant and has not occurred by chance.

Conclusion:

We conclude that there is an increased frequency of higher fasting blood glucose in hypothyroid patients. This study shows that the hypothyroid condition will causes overall higher average fasting blood glucose than normal.

POST PRANDIAL BLOOD SUGAR

Data:



Discussion:

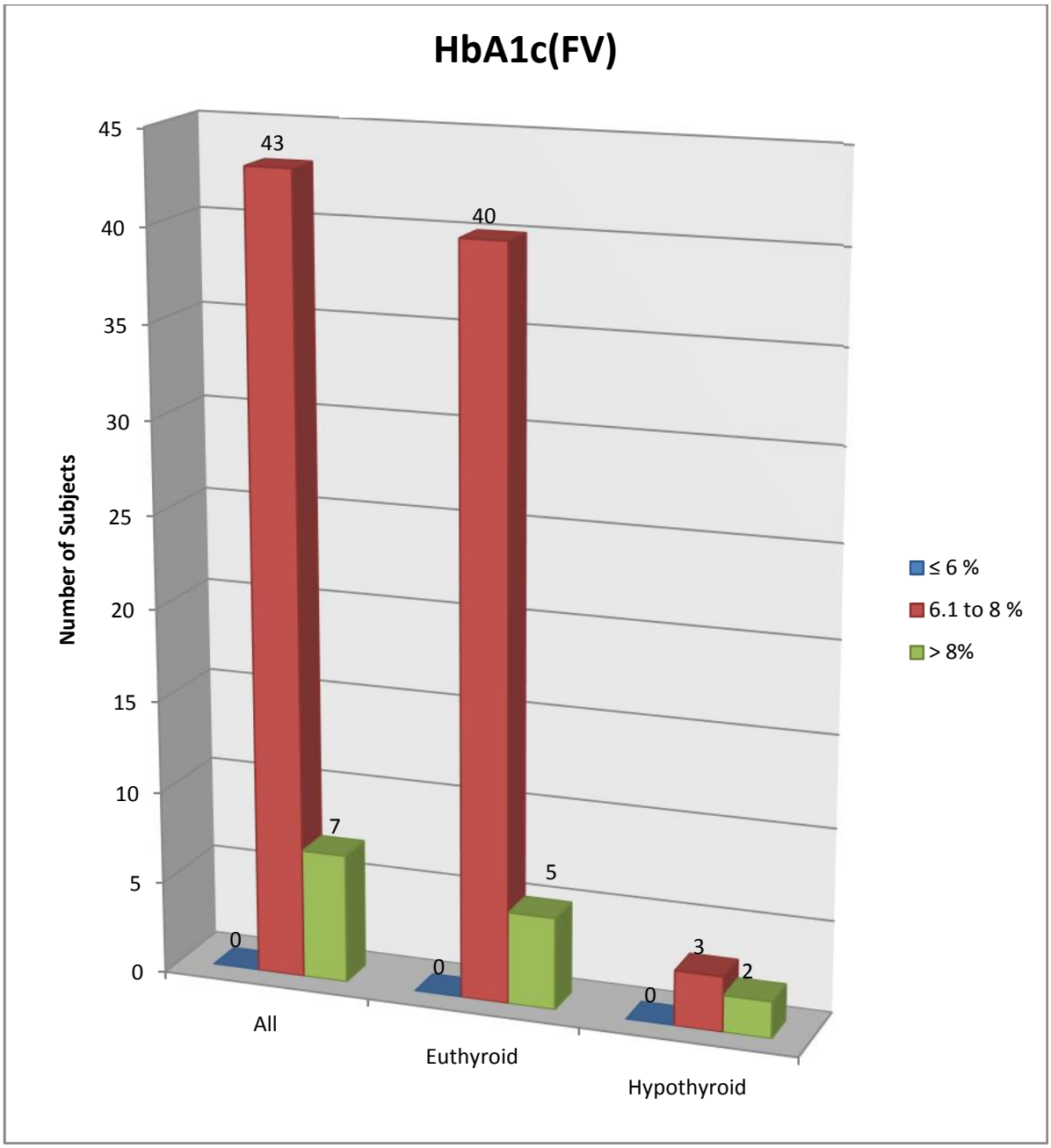
Post Prandial Blood Sugar	All	%	Euthyroid	%	Hypothyroid	%
≤ 150 mg/dl	17	34	16	35.56	1	20
151 to 200 mg/dl	30	60	27	60.00	3	60
> 200 mg/dl years	3	6	2	4.44	1	20
Total	50	100	45	100	5	100

Post Prandial Blood Sugar	Euthyroid	Hypothyroid
N	45	5
Mean	159.40	172.60
SD	20.64	26.62
P value Unpaired t test	0.3366892	

By conventional criteria the association between the study groups and post prandial is considered to be not statistically significant since $p > 0.05$.

HbA1c (Fasting Value)

Data:



Discussion:

HbA1c(FV)	All	%	Euthyroid	%	Hypothyroid	%
≤ 6 %	0	0	0	0.00	0	0
6.1 to 8 %	43	86	40	88.89	3	60
> 8%	7	14	5	11.11	2	40
Total	50	100	45	100	5	100

HbA1c(FV)	Euthyroid	Hypothyroid
N	45	5
Mean	7.54	8.76
SD	0.49	0.59
P value Unpaired t test	0.0022491*	

By conventional criteria the association between HBA1c-Fasting value and hypothyroidism is considered to be statistically significant since $p < 0.05$.

Statistical Significance:

This indicates that there is a true difference among the study groups and the difference is significant.

In simple terms, while assessing the prevalence of hypothyroidism in diabetes mellitus, the average HBA1c-Fasting value is 7.54% in euthyroid patients compared with 8.76% in hypothyroid patients with a p-value of 0.0022491 according to Unpaired t- test.

Clinical Significance:

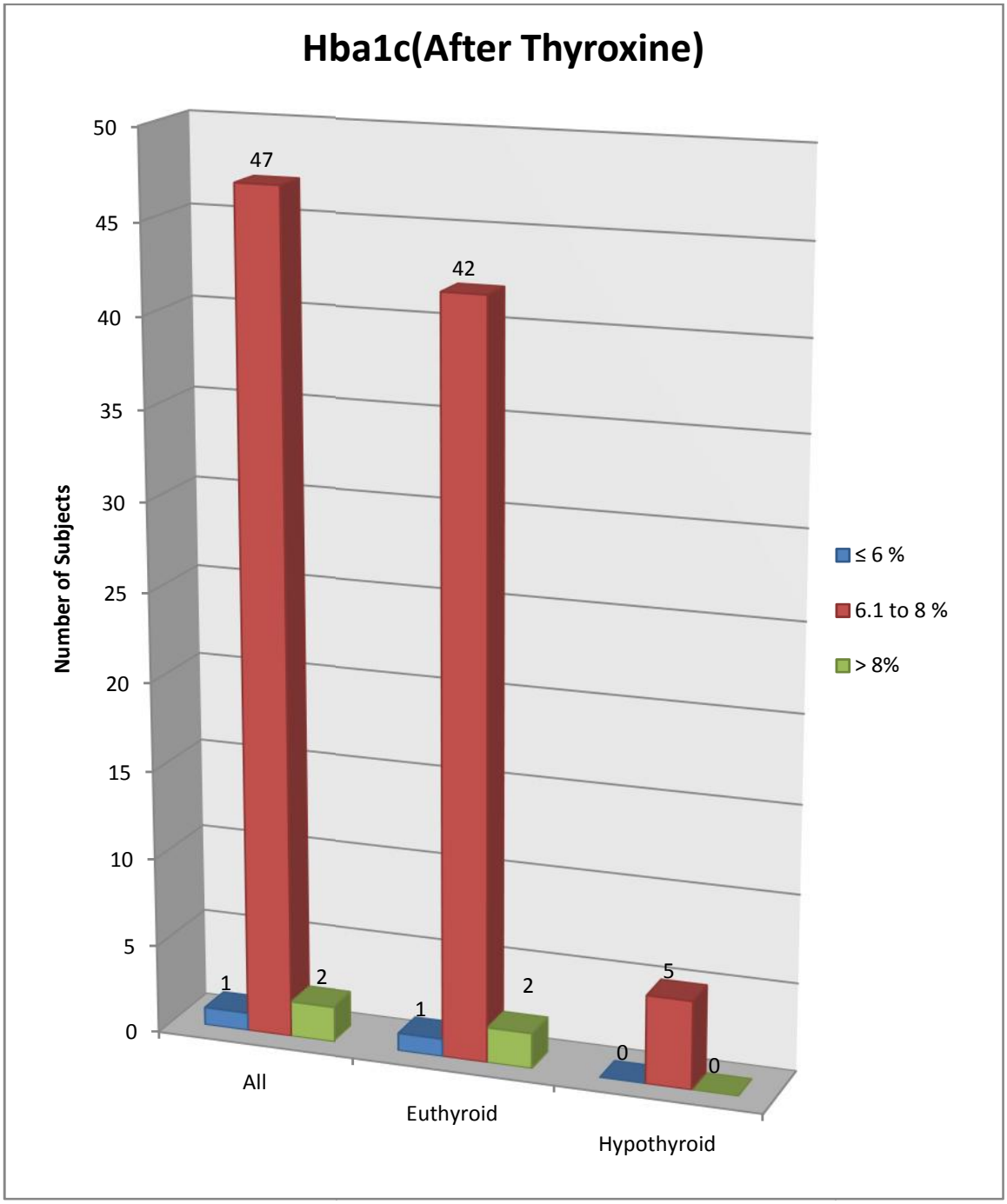
The average HBA1c-Fasting value is meaningfully less (2.89%) in euthyroid patients compared to hypothyroid patients by a difference of 1.22%. This difference is true and significant and has not occurred by chance.

Conclusion:

We conclude that there is an increased frequency of higher HBA1c-Fasting value in hypothyroid patients. This study shows that the hypothyroid condition will cause an overall higher average HBA1c-Fasting value than normal.

Hba1c (After Thyroxine)

Data:



Discussion:

Hba1c(After Thyroxine)	All	%	Euthyroid	%	Hypothyroid	%
≤ 6 %	1	2	1	2.22	0	0
6.1 to 8 %	47	94	42	93.33	5	100
> 8%	2	4	2	4.44	0	0
Total	50	100	45	100	5	100

Hba1c(After Thyroxine)	Euthyroid	Hypothyroid
N	45	5
Mean	7.18	7.24
SD	0.42	0.62
P value Unpaired t test	0.033053*	

By conventional criteria the association between HBA1c-After Thyroxine value and hypothyroidism is considered to be statistically significant since $p < 0.05$.

Statistical Significance:

This indicates that there is a true difference among the study groups and the difference is significant.

In simple terms, while assessing the prevalence of hypothyroidism in diabetes mellitus, the average HBA1c-After Thyroxine value is 7.18% in euthyroid patients compared with 7.24% in hypothyroid patients with a p-value of 0.033053 according to Unpaired t- test.

Clinical Significance:

The average HBA1c- After Thyroxine value is meaningfully less (0.89%) in euthyroid patients compared to hypothyroid patients by a difference of 0.06%. This difference is true and significant and has not occurred by chance.

Conclusion:

We conclude that there is a decreased frequency of higher HBA1c- After Thyroxine value in hypothyroid patients compared to HBA1c-Fasting values. This study shows that the corrected hypothyroid condition will cause a lower average HBA1c- After Thyroxine value very near to normal.

HBA1c Levels	Mean (Euthyroid)	Mean (Hypothyroid)
HBA1c Fasting Value	7.54 mg/dl	8.76 mg/dl
HBA1c After Thyroxine Value	7.18 mg/dl	7.24mg/dl
P value **Paired t-test**	0.0000*	0.0138*
Pearson Correlation	0.783429338	0.895299319

By conventional criteria the association between HBA1c-Fasing and After Thyroxine values are considered to be statistically significant since $p < 0.05$.

The average HBA1c- After Thyroxine value is meaningfully less (21%) in hypothyroid patients compared to HBA1c Fasting values by a difference of 1.52% with a p-value of 0.0138 according to Paired t-test.. This difference is true and significant and has not occurred by chance.

There is a strong positive correlation between HBA1c-Fasing and After Thyroxine values among Hypothyroids in diabetes mellitus subjects in our study. This is indicated by the Pearson's R Correlation value of 0.895299319. The increase inHBA1c levels among diabetics correlates positively, directly and strongly with the increase in hypothyroid status this means as the hypothyroid status increases as the HBA1c values increase.

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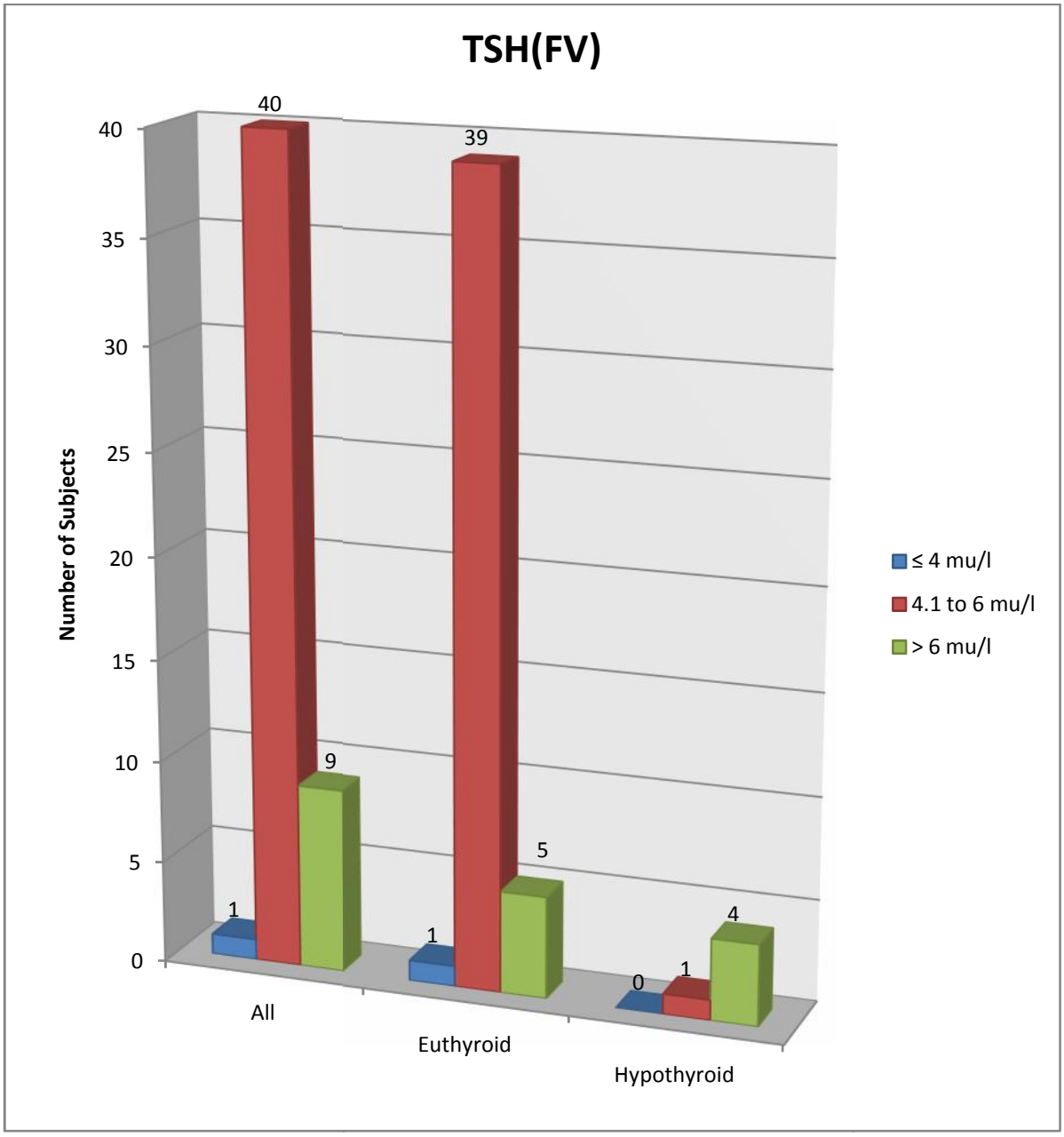
TSH (Fasting Value)

Data:



Discussion:

TSH(FV)	All	%	Euthyroid	%	Hypothyroid	%
≤ 4 mu/l	1	2	1	2.22	0	0
4.1 to 6 mu/l	40	80	39	86.67	1	20
> 6 mu/l	9	18	5	11.11	4	80
Total	50	100	45	100	5	100

TSH(FV)	Euthyroid	Hypothyroid
N	45	5
Mean	5.58	6.94
SD	0.64	0.86
P value Unpaired t test	0.0222323*	

By conventional criteria the association between TSH-Fasting value and hypothyroidism is considered to be statistically significant since $p < 0.05$.

Statistical Significance:

This indicates that there is a true difference among the study groups and the difference is significant.

In simple terms, while assessing the prevalence of hypothyroidism in diabetes mellitus, the average TSH-Fasting value is 5.58 mu/l in euthyroid patients compared with 6.94 mu/l in hypothyroid patients with a p-value of 0.0222323 according to Unpaired t- test.

Clinical Significance:

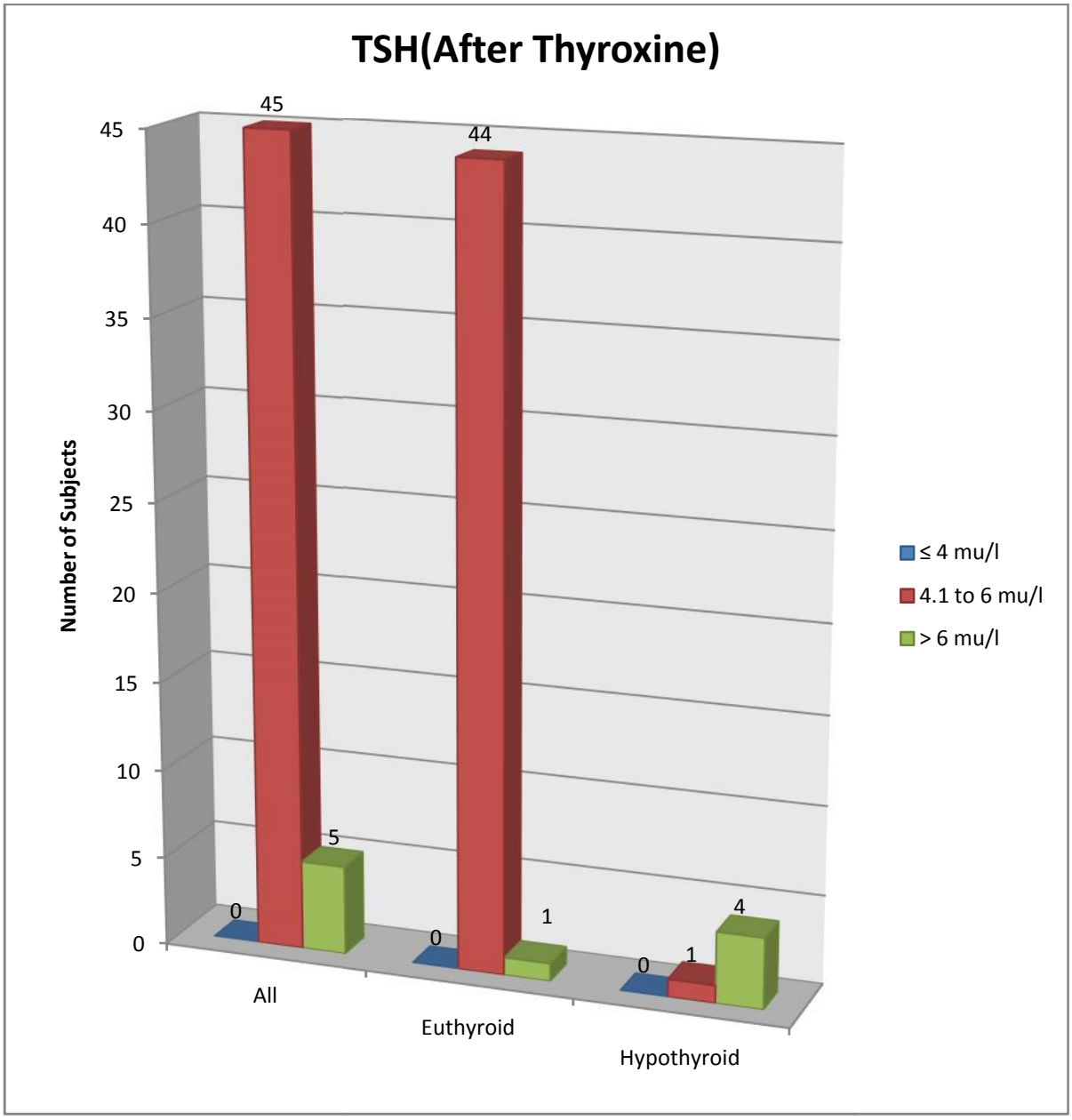
The average HBA1c-Fasting value is meaningfully less (24.42%) in euthyroid patients compared to hypothyroid patients by a difference of 1.36 mu/l. This difference is true and significant and has not occurred by chance.

Conclusion:

We conclude that there is an increased frequency of higher TSH-Fasting value in hypothyroid patients. This study shows that the hypothyroid condition will cause an overall higher average TSH-Fasting value than normal.

TSH (After Thyroxine)

Data:



Discussion:

TSH(After Thyroxine)	All	%	Euthyroid	%	Hypothyroid	%
≤ 4 mu/l	0	0	0	0.00	0	0
4.1 to 6 mu/l	45	90	44	97.78	1	20
> 6 mu/l	5	10	1	2.22	4	80
Total	50	100	45	100	5	100

TSH(After Thyroxine)	Euthyroid	Hypothyroid
N	45	5
Mean	5.42	5.74
SD	0.34	0.76
P value Unpaired t test	0.0173477*	

By conventional criteria the association between TSH-After Thyroxine value and hypothyroidism is considered to be statistically significant since $p < 0.05$.

Statistical Significance:

This indicates that there is a true difference among the study groups and the difference is significant.

In simple terms, while assessing the prevalence of hypothyroidism in diabetes mellitus, the average TSH-After Thyroxine value is 5.42 mu/l in euthyroid

patients compared with 5.74 mu/l in hypothyroid patients with a p-value of 0.0173477according to Unpaired t- test.

Clinical Significance:

The average TSH- After Thyroxine value is meaningfully less (5.86%) in euthyroid patients compared to hypothyroid patients by a difference of 0.32 mu/l This difference is true and significant and has not occurred by chance.

Conclusion:

We conclude that there is a decreased frequency of higher TSH- After Thyroxine value in hypothyroid patients compared to TSH-Fasting values. This study shows that the corrected hypothyroid condition will cause a lower average TSH- After Thyroxine value very near to normal.

TSH Levels	Mean (Euthyroid)	Mean (Hypothyroid)
HBA1c Fasting Value	5.58 mu/l	6.94 mu/l
HBA1c After Thyroxine Value	5.42 mu/l	5.74 mu/l
P value **Paired t-test**	0.03762*	0.01161*
Pearson Correlation	0.129498659	0.969915853

By conventional criteria the association between HBA1c-Fasing and After Thyroxine values are considered to be statistically significant since $p < 0.05$.

The average TSH- After Thyroxine value is meaningfully less (20.9%) in hypothyroid patients compared to TSH Fasting values by a difference of 1.2 mu/l with a p-value of 0.01161 according to Paired t-test.. This difference is true and significant and has not occurred by chance.

There is a strong positive correlation betweenTSH-Fasting and After Thyroxine values among Hypothyroids in diabetes mellitus subjects in our study. This is indicated by the Pearson's R Correlation value of 0.969915853. The increase in TSH levels among diabetics correlates positively, directly and strongly with the increase in hypothyroid status this means as the hypothyroid status increases as the TSH values increase.

VI. CITATIONS

1. Leu wei et al at capital medical university in Beijing's Tongren hospital did a study to find out the effect of subclinical hypothyroidism on diabetes mellitus and on glucose metabolism where they followed up 1170 cases of type 2 diabetes mellitus with subclinical hypothyroidism. They found that in their study population the hypothyroid patients with subclinical hypothyroidism had significant abnormalities in glucose metabolism like control of fbg,ppbg,hba1c and they found significant positive correlation ($p<.001$) between the parameters.
2. Zeleja Velija-Asimi et al at University Clinical Centre, Sarajevo performed a trial to study the effects of subclinical hypothyroidism on effects of subclinical hypothyroidism on metabolic control and hyperinsulinemia. The study included 53 patients of which 12 patients had type 2 diabetes mellitus. They followed up the patients for 6 months after administering L-thyroxine. They found a better control of FBS, PPBS and HbA1C and fasting lipid profile. They found a positive correlation($r=0.41$) between HBA1C and TSH and positive correlation between HBA1C and insulin($r=0.35$).Thus they concluded that normalised TSH levels will result in decreased levels of fasting insulin, FBS, PPBS and HBA1C.
3. Edina Bilic-Komarica et al conducted a study to understand the effects of treatment of L-thyroxine on glucose regulation in patients with subclinical hypothyroidism. The study group consisted of 100 patients out of which 38

patients were diabetic. The patients were followed up after 6 months of L-thyroxine (25-50mcg) and physical activity and tests performed were T3, T4, TSH, HBA1C, CRP, and insulin and lipid levels. After 6 months testing showed significantly reduced FBS,PPBS,HBA1c(r=0.46),fasting insulin and lipids thus concluding that normalising TSH levels with thyroxine treatment will control blood sugar better than other groups.

4. CEJ Udiong et al studied the glycaemic indices and thyroid hormone in type 1 and type Diabetes Mellitus.18 type 1 and 143 type 2 diabetic patients were enrolled in the study and FPG, HBA1c and c peptide levels were assayed. Correlation of HBA1c and TSH had significant correlation ($r=0.211$, $p<0.1$) in type 2 diabetes while in type 1 diabetes there was negative association.
5. Zhao jin Liang et al studied the relationship between glycosylated haemoglobin and thyroid hormones in type 2 diabetes patients and found a positive correlation between HBA1c and TSH levels, T3 and T4 levels and correlation was found to be statistically significant ($p<.01$).So conclusion was made that thyroid hormones improve with appropriate blood sugar control in type 2 diabetes mellitus patients.
6. SAP Chubb et al studied the prevalence and progression of subclinical hypothyroidism in women with type 2 diabetes. They did a cross sectional and longitudinal observational study on 420 randomly assigned females. TSH, free T4 and TPO antibodies, HBa1c and, glucose and lipid profile was measured. The prevalence of hypothyroidism was found to be 8.6 %(after

excluding the already hypothyroid patients. So they concluded that subclinical hypothyroidism was an incidental finding in type 2 diabetes and routine screening was questionable.

7. Abdal Rahman M. Radaideh et al from Jordan studied the prevalence of thyroid dysfunction and autoimmunity in type 2 diabetic patients. A group of 908 patients were investigated and underwent thyroid function tests. As a result of this study 6.6% of the patients were diagnosed newly with hypothyroidism of which 4.1 % ($p<0.5$) had subclinical hypothyroidism. Anti tpo was positive in 8.3%.Thus the study suggested that diabetic patients should be screened for hypothyroidism.
8. Mohammed Afdhami-Ardekani et al studied effect of metabolic response in type 2 diabetes patients. They used thyroid function tests, lipid profile and glycated haemoglobin in type 2 diabetic patients and cross sectional study was carried out on1200 patients. Study concluded that higher proportion of type 2 diabetes patients have thyroid dysfunction and more of metabolic disturbances ($p<0.02$).
9. Avraham Ishay et al studied the prevalence of subclinical hypothyroidism in women with type 2 diabetes mellitus.410 women with type 2 diabetes and 125 non diabetic patients were included in the study found in their study that routine screening is not warranted($p=0.3$,$p=0.75$)as the prevalence of hypothyroidism in both study and control groups were similar.

10. E. Maratou et al performed to correlate the study of insulin resistance and insulin related glucose transport in patients with clinical and subclinical hypothyroidism.3 groups of patients one euthyroid, one hypothyroid and one sub clinical hypothyroid were studied by assessing the metabolism of insulin both in vivo and in vitro. The results showed that insulin resistance was more hypothyroid and subclinical hypothyrosis patients and insulin stimulated glucose transport via GLUT4 was impaired. So these findings also suggested increased incidence of insulin resistance disorders in thyroid patients.
11. V Uppal et al studied the existence of thyroid dysfunction in type 2 diabetic patients in people of north India and correlate thyroid hormones with serum insulin and HBa1c.A case control study was carried out on117 adults of same age group. The study showed significant relation between HBa1c and thyroid hormones but no relation between thyroid hormones and insulin levels.
12. HA Begum et al studied the co-occurrence of type 2 diabetes and thyroid metabolic disorders.50 type 2 diabetes patients were studied and T3, T4, TSH, anti tpo were studied in diabetic patients and correlated with HBa1c, FPG, and PPBG. The study showed significant low free T3 (free T3 syndrome) in diabetic patients (p=0.00) in which there was no thyroid autoimmunity.

VII. CONCLUSION

Diabetes Mellitus and hypothyroidism are very closely related to each other and both are associated with several metabolic abnormalities. There are many common features in both these endocrine disorders.

The normalization of TSH levels leads to a reduction in postprandial glucose levels, CRP, HbA1c and lipids. This indicates a significant effect of treatment with L-thyroxine on glycemic control in patients with subclinical hypothyroidism.

Determination of TSH is accurate, accessible, safe and inexpensive test to diagnose subclinical hypothyroidism. Determining the level of TSH can be used to define the risk of the occurrence of various complications (osteoporosis, cardiovascular disease, depression) for different intervals between TSH.

Subclinical hypothyroidism is quite hard to diagnose. In practice this is often overlooked. Adequate diagnosis requires conducting extensive laboratory tests other than routine as the TSH test. Monitoring of body temperature and careful monitoring of clinical signs, then well taken case history helps to faster and easier detection of this disease in medical practice.

My study revealed a strong correlation between duration of diabetes and hypothyroidism, FBS values and hypothyroidism.Hba1c before and after thyroxine, TSH before and after thyroxine also revealed a strong

coreelation($p<.05$).The main part of my study which revealed a strong correlation between Hba1c and TSH levels.

As per the previous studies (as in citations) and my study, I can conclude that there was high prevalence of hypothyroidism in diabetes mellitus and there was correlation between Hba1c and TSH levels.

More studies with similar indices have to be performed to confirm the study results. I can also conclude that doing a TSH levels in patients of diabetes mellitus is warranted.

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PROFORMA

NAME	
AGE /SEX:	
OCCUPATION:	
ADDRESS WITH CONTACT NO:	
IP NO/OP NO:	
DATE OF ADMISSION:	
DATE OF DISCHARGE	

Swelling in neck		Fatigue	
Hoarse voice		Menstrual disturbances	
Constipation			
Weight gain& reduced appetite		h/o diabetes	
Cold intolerance		h/o hypothyroidism	

Pallor		CVS	
Icterus		RS	
Pedal edema		P/A	
Ophthal examination		CNS	
Pulse		BP	

Examination of neck

INVESTIGATIONS

TC	DC	ESR	HB	PCV	MCV	MCH	MCHC	PLT

SUGAR FBS PPBS	UREA	CR	Na+	K+	HCO3-	Cl-

TB	DB	SGOT	SGPT	SAP	TOTAL PROTEINS	ALBUMIN

TSH	FT3	FT4

HBA1C

GOVT.STANLEY MEDICAL COLLEGE, CHENNAI- 600 001

INFORMED CONSENT

DISSERTATION TOPIC: "A STUDY ON PREVALENCE OF HYPOTHYROIDISM (CLINICAL/SUBCLINICAL) IN DIABETES MELLITUS AND CORRELATION OF HbA1C LEVELS WITH TSH LEVELS"

PLACE OF STUDY: GOVT. STANLEY MEDICAL COLLEGE, CHENNAI

NAME AND ADDRESS OF PATIENT:

I, _____ have been informed about the details of the study in my own language.

I have completely understood the details of the study.

I am aware of the possible risks and benefits, while taking part in the study.

I understand that I can withdraw from the study at any point of time and even then, I will continue to receive the medical treatment as usual.

I understand that I will not get any payment for taking part in this study.

I will not object if the results of this study are getting published in any medical journal, provided my personal identity is not revealed.

I know what I am supposed to do by taking part in this study and I assure that I would extend my full co-operation for this study.

Name and Address of the Volunteer:

Signature/Thumb impression of the Volunteer

Date:

Witnesses:
(Signature, Name & Address)

Date:
Name and signature of investigator:

சர்க்கரை நோய உள்ளவர்களுடையே ஹைபோதைராயடு நோயின தாக்கததையும், இரததததில HbA1c மறறுய TSH அளவுகளுடையே ஆன தொடர்பையும் அறிவதற்கான ஓர ஆயவு

ஆயவாளர:**மரு. திலிப ஹரிநரன வெலலததோள,**

முதுநிலைபடடமேறபடிபபுமாணவர,

பொதுமருததுவ படடபபடிபபு.

வழிகாடடி :**பேராசிரியரமரு. க.சுநதரமூரதி** ,

பொதுமருததுவபேராசிரியர,அரசு படாலிமருததுவமனை.

சுயஒபபுதலபடிவய

பெயர: வயது: உளளுருபபுஎண:

இநத மருததுவ ஆயவின வரைமுறைகள எனக்கு வளக்கபபடடது. எனதுடைய சந்தேகங்களைக்கேட்கவும்,அதறகான தகுநதவிளக்கங்களைபபெறவும் வாயபபளிக்கபபடடது.

நான இவவாயவில தனனிசசையாகததான பஙகேறகிறேன. எநத காரணததினாலும ,எநதகடடதிலும, எநத சட்டசிக்கலும் இலலறி இநத ஆய்வலிருந்து விலகிக்கொளளலாம எனபதை அறிநதுகொணடேன.

நான ஆயவிலிருநது வலகிகொணடாலும ஆயவாளர எனதுடைய மருததுவ அறிக்கைகளைப்பார்ப்பதறகோ அலலது உபயோகிக்கவோ என அனுமதி தேவையிலலை எனவும அறிந்துகொணடேன்.எனனைபபறறிய தகவலகள இரகசியமாகபபாதுகாக்கபபடும எனபதையும அறிவேன.

இநத ஆயவின மூலம கிடைக்கும தகவலகளையும பரிசோதனை முடிவுகளையும .ஆயவாளர அவர வெளியிடுவதறகேற்ப எவவிதமாகப்பயனபடுத்திகொளளவும, அதனைபபிரசுரிக்கவும் முழுமனதுடன சமமதிக்கிறேன.

இநத ஆயவில பஙகு கொளள ஒபபுகொணகிறேன. எனக்குகொடுக்கபபடட அறிவுரைகளினபடி நடநதுகொளவதுடன, ஆயவாளருக்கு உணமையுடன இருப்பேன எனதும உறுதியளிக்கிறேன் .என உடல்நலம பாதிக்கப்படடாலோ அலலது வழக்கமதறகு மாறானநோய்க்குறிதெனபடடாலோ உடனே அதை தெரிவிபபேன என உறுதிகூறுகிறேன.

இநத ஆயவில எனக்கு எவவிதமான பரிசோதனைகளையும, சிகிசசைகளையும மேறகொளள நான முழுமனதுடன சமமதிக்கிறேன்.

இபபடிக்கு

நோயளியினகையொபப பெயர

ஆயவாளரகையொபப பெயர
(மரு. **திலிப ஹரிந்ரன வெலலததோள**)

சர்க்கரை நோய உள்ளவர்களுடையே ஹைபோதைராயடு நோயின தாக்கததையும், இரததததில HbA1c மறறுய TSH அளவுகளுடையே ஆன தொடர்பையும் அறிவதற்கான ஓர ஆயவு

ஆயவாளர:**மரு. திலிப ஹரஹரன வெலலததோட**,

முதுநிலைபடடமேறபடிபபுமாணவர,

பொதுமருததுவ படடபபடிபபு.

வழிகாடடி : **பேராசிரயர மரு. க.சுநதரமூரதி** ,

பொதுமருததுவ பேராசிரயர,

அரசு படாலிமருததுவமனை.

பஙகேறபாளரகளுகான தகவலபடிவம

நஙக இநத ஆயவில பஙகேறக அழைகபபடுகிறரக. இநத ஆயவில பஙகேறகுமுன, இதன நோக்கதையும, முறைகளையும ,இதனால ஏறபடும் பினவிளைவுகளையும் நங்கள அறிநது கொள ஆயவாளர அளிகுய தகவல:

உஙக நோயின வரலாறறும, உஙகளின முழு உடலபரசோதனையும தெளவாகவும வரசாவாகவும பதிவுசெயயபபடும.

இநத ஆயவின முடிவுக மருததுவ காரணஙகளுகாகவும, மருததுவ கலவிகாகவும பயனபடுத்தப்படும். இந்த ஆய்வு பறறிய சநதேகங்களுகு உரிய முறையில விளகமளிகபபடும. தஙகளைப்பற்றிய தகவலக இரகசியமாக பாதுகாகப்படும.

இநத ஆயவில இருநது எபபோது வேணடுமானாலும தஙக எவவித முனனறிவிபபினறியும, எவவித சட்டசிகலும இனறி வலகிகொளளலாம.

இநத ஆயவில பஙகேறகுமாறு கேடுகொளகிறேன.

நனறி,

ஆயவாளர கையொபப நோயாளியின கையொபப

(மரு. **திலிப ஹரஹரன வெலலததோ**) (பெயர:)

ETHICAL COMMITTEE APPROVAL

INSTITUTIONAL ETHICAL COMMITTEE,
STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work : A Study on prevalence of Hypothroidism (Clinical/Sub Clinical) in Diabetes mellitus and correlation of Hb a1c levels with TsH levels

Principal Investigator : Dr. Dilip Harindran Vallathol

Designation : PG in MD (General Medicine)

Department : Department of General Medicine
Government Stanley Medical College,
Chennai-01

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 05.08.2014 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

K Vasanthan
MEMBER SECRETARY,
IEC, SMC, CHENNAI

MASTER CHART

SlNo	Age	Sex	H/O diabetes	H/O hypot	FBS (MG/DL)	PPBS (MG/DL)	HbA1c (FV) (%)	TSH(FV) (mIU/L)	TSH (AT)	Hba1c (AT)
1	54	F	YES(5 YRS)	NO	102	186	8	6	5	7
2	58	F	YES(6YRS)	NO	96	156	7.5	6.8	4.8	6
3	62	F	YES(4YRS)	NO	100	139	8.5	7	5.8	8
4	55	M	YES(7YRs)	NO	123	198	8.3	7.2	6.5	7.9
5	50	F	YES(3YRS)	NO	109	176	6.5	5.5	5.2	6.5
6	56	F	YES(5 YRS)	NO	114	154	7	6	5.4	6.8
7	57	F	YES(8YRS)	NO	122	201	8.5	6.7	6	7.7
8	47	M	YES(4YRS)	NO	103	139	7.2	4.8		
9	50	M	YES(5YRS)	NO	121	178	7.8	5.9	5.2	7.3
10	65	F	YES(10YRS)	YES	134	202	8.4	7.8	7.2	7.5
11	49	M	YES(3YRS)	NO	100	130	6.7	5.7	5.3	6.6
12	51	F	YES(5YRS)	YES	98	129	6.9	7.8	7.7	6.2
13	56	F	YES(6YRS)	NO	104	164	7.1	5.9	5.4	6.9
14	55	F	YES(7YRS)	NO	108	156	7.4	5.7	5.4	7
15	60	M	YES(9YRS)	NO	106	143	7	5.5	5	6.9
16	54	F	YES(6YRS)	NO	101	132	7	5.3	5.2	7
17	61	M	YES(11YRS)	NO	120	190	8	6.1	5.9	7.5
18	67	F	YES(13YRS)	YES	119	176	8.2	6.8	6.7	7.8
19	58	F	YES(7YRS)	NO	110	138	7.5	5.8	5.7	7.2
20	49	F	YES(4YRS)	NO	108	140	7.3	4.9		
21	43	F	YES(3YRS)	NO	94	120	7	5.3	5	7
22	62	M	YES(12YRS)	NO	124	190	8.8	6	5.5	8.2
23	56	F	YES(6YRS)	NO	105	149	7.6	5.8	5.4	7.3
24	55	F	YES(5YRS)	NO	103	145	7.4	5.5	5.2	7
25	58	M	YES(8YRS)	NO	117	168	7.5	5.8	5.5	7.2
26	52	F	YES(6YRS)	NO	106	134	7.3	5.5	5.3	7.1
27	51	F	YES(3YRS)	NO	109	140	7.6	4.8		
28	52	F	YES(5YRS)	NO	110	164	7.8	5.9	5.6	7.5
29	57	F	YES(6YRS)	NO	118	176	7.9	6	5.8	7.6
30	58	M	YES(5YRS)	NO	120	164	7.6	4		
31	57	F	YES(6YRS)	NO	118	172	7.4	5.6	5.2	7.2
32	64	M	YES(5YRS)	NO	116	166	7.5	5.4	5.2	7.2
33	55	F	YES(4YRS)	NO	123	185	7.6	5.5	5.2	7.3
34	57	M	YES(9YRS)	NO	121	175	7.8	4.7		
35	58	F	YES(7YRS)	NO	115	154	7	4.5		
36	56	M	YES(6YRS)	NO	113	145	7.4	5.6	5.4	7.2
37	58	F	YES(7YRS)	NO	121	167	7.5	4.9		
38	57	M	YES(8YRS)	NO	124	163	7.6	5.6	5.4	7.2
39	58	F	YES(7YRS)	NO	113	143	7.5	4.3		

40	59	F	YES(6YRS)	NO	112	154	7.6	5.6	5.3	7.3
41	56	F	YES(5YRS)	YES	122	178	7.7	6.5	6.4	7.5
42	58	M	YES(7YRS)	NO	134	206	8.7	5.8	5.5	8.3
43	47	F	YES(3YRS)	NO	110	156	7	5.5	5.2	6.8
44	49	F	YES(5YRS)	NO	100	140	7	4.7		
45	53	F	YES(4YRS)	NO	101	134	7.4	5.4	5.2	7.2
46	56	F	YES(5YRS)	YES	122	178	7.6	5.8	5.7	7.2
47	53	F	YES(5YRS)	NO	114	154	7.5	5.5	5.3	7.3
48	54	M	YES(5YRS)	NO	112	153	7.7	5.8	5.4	7.4
49	59	F	YES(7YRS)	NO	119	156	7.5	5.4	5.2	7.2
50	60	M	YES(10YRS)	NO	120	180	7.9	5.8	5.4	7.5

KEY TO MASTER CHART

FBS : Fasting Blood Sugar

PPBS : Post Prandial Blood Sugar

TSH : Thyroid Stimulating Hormone

HbA1c : Glycosylated Haemoglobin

Hypot : Hypothyroidism

AT : After thyroxine treatment of three months